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Impact of cardiovascular counseling and screening in Hodgkin lymphoma survivors

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Abstract

Purpose

Cardiovascular disease (CVD) is the most common nonmalignant cause of death in Hodgkin lymphoma (HL) survivors, especially after mediastinal irradiation. The role of screening for CVD in HL survivors is unclear, but confrontation with risks of CVD may have a negative influence on health-related quality of life (HRQL). As part of a phase II screening study using computed tomography angiography (CTA) among HL survivors, a HRQL analysis was done to evaluate the emotional and practical burden and perceived benefits of screening and the effect of CVD-specific counseling on patient satisfaction.

Methods

Patients who participated in the screening study took also part in the HRQL study. The impact of undergoing screening was evaluated with a 9-item questionnaire, and impact on HRQL with the EORTC QLQ-C30. The effect of counseling on CVD on perceived information provision was evaluated with the EORTC INFO-25. All questionnaires were completed at baseline and after screening.

Results

Baseline questionnaires were received from 48 participants, and 43 completed questionnaires after screening. Mean age was 47 years, mean time since diagnosis 21 years. 93% were content with participating, and 80% did not find the emphasis placed on late effects burdensome, although screening did have a small impact on social functioning and global quality of life.

Perceived information on disease, medical tests and treatment increased significantly after screening ($p < 0.01$). Differences were clinically relevant. There were no differences in perceived information between patients with and without screen-detected CVD.

Conclusions

Screening was evaluated favorably, whether CTA showed abnormalities or not. Extensive counseling resulted in substantially increased information provision, resulting in improved information satisfaction. Screening by means of CTA and subsequent cardiac intervention was highly valued and the benefits were felt to outweigh the emotional and practical burden.

Introduction

The outlook for cure of Hodgkin lymphoma (HL) patients has improved dramatically due to modern chemotherapy and improved radiotherapy techniques (1-3). However, over the past decade it has become evident that cure may come at a price. Epidemiological studies have shown that survivors of HL are at serious risk for late treatment effects, such as an increased risk of long-term risk of secondary cancers (4, 5). The most common nonmalignant long-term complication of treatment in HL survivors is cardiovascular disease (CVD). HL survivors who had mediastinal radiotherapy have a 3-4 fold increased risk of myocardial infarction due to coronary artery disease (CAD) (6-9). Even severe CAD is often not accompanied by symptoms, and can occur in absence of traditional risk factors (10).

The role of screening for radiation-induced CAD in HL survivors is unclear. Several prospective studies have shown that screening asymptomatic HL survivors by means of computed tomographic coronary angiography (CTA) yields high prevalence rates of CAD (11-13).

However, the benefit of screening on survival is unknown. Also, the perceived burden and distress of undergoing screening, and the effect of cardiovascular counseling on health-related quality of life (HRQL) have not been studied in HL survivors. Confrontation with possible risks of disease may have a negative effect on psychosocial well-being. This effect has been shown in screening programs for breast cancer (14). However, other studies have shown that empowering patients by improving information provision and thus disease understanding might actually improve HRQL (15).

To investigate the role of CTA as a screening tool, we have conducted a phase II screening study in asymptomatic HL survivors at risk for developing radiation-induced CAD (16). We included a HRQL analysis to determine the perceived burden of screening, and evaluate whether extensive counseling on risks of CVD improved perceived information provision and patient satisfaction.

Methods

Patients

The study protocol for this phase II screening protocol was approved by the Leiden University Medical Center (LUMC) Ethics Committee and registered with Clinical-

Trials.gov, NCT01271127. Since 2010 long-term HL survivors from regular follow-up outpatient clinics at the Department of Radiation Oncology at LUMC are referred to an outpatient clinic specifically designed for monitoring late effects of treatment of HL. At this outpatient clinic two dedicated radiation oncologists and one hematologist counsel HL survivors who are at least 5 years disease-free after treatment with respect to individual risks of late treatment effects, and provide standardized follow-up care, including screening for breast cancer in female HL survivors.

To address the feasibility of cardiac screening by means of CTA and evaluate the perceived burden and benefits of screening a phase II study was designed. Patients attending the late effects outpatient clinic who were at least 10 years disease free and had received mediastinal radiotherapy as part of their treatment, who were < 60 years, and without current serious cardiac disease were eligible, and invited to participate in the study.

Primary endpoint of the phase II study was the presence of significant CAD (> 50% stenosis) on CTA. Patients with abnormal CTA scans subsequently underwent diagnostic coronary angiography (CAG). CTA screening was considered to be indicated for testing in a larger population if revascularization would be indicated in \geq 12% of the patients undergoing CTA. Secondary objectives were to determine the frequency and type of subsequent interventions, to evaluate satisfaction with information provision and to determine the burden of the various aspects of screening and the impact of specific counseling on CVD on HRQL.

Counseling, screening and assessment of HRQL

Participants in the screening study received specific, in-depth counseling on the risk of developing radiation-induced CVD by a dedicated radiation oncologist. After written informed consent, patients were referred to the cardiology outpatient clinic where they received additional counseling and lifestyle advice to reduce the risk of future cardiac disorders by a cardiologist. Subsequently an extensive cardiovascular screening program was performed. This included a resting electrocardiogram (ECG), echocardiography and symptom-limited exercise ECG testing. CTA was performed in a separate visit. After completing all tests, results and potential indications for future analysis or treatment were discussed. Participation in the HRQL part of the screening study was not mandatory for inclusion in the cardiac screening program.

For the HRQL part, patients were asked to complete three validated questionnaires at baseline and after discussing test results or subsequent interventions; a 9-item screening-specific questionnaire was added to the end-of-screening questionnaire. Baseline questionnaires were handed out at the time patients were asked to

participate in the screening study and were returned prior to referral to the Cardiology Department. End of study questionnaires were sent out 1-2 months after the final visit to the Cardiology department.

Questionnaires

To evaluate the effect of cardiovascular counseling and screening on information provision the EORTC INFO-25 questionnaire was used. This module evaluates cancer patient satisfaction with regard to information received in different areas of their disease and treatment, and evaluates qualitative aspects (17, 18). The 25 items are organized in four multi-item scales and single items. After linear transformation, all scores range from 0-100 (19). High scores mean a high level of information received (17).

Global quality of life was assessed with the EORTC quality of life core questionnaire (QLQ C-30 v3.0). All subscales and symptom responses from this questionnaire are linearly converted to 0 to 100 scales (19). A higher score for a functional or global quality of life scale represents a better level of functioning.

Fatigue was measured with the fatigue assessment scale (FAS); a validated 10 item questionnaire reflecting mental and physical fatigue (20, 21). Total scores ranged from 10 to 50. A higher score reflects a higher level of fatigue. A score over 21 points indicates a substantial level of fatigue (20).

Evaluation of screening

To evaluate the burden of the various aspects of screening, and determine satisfaction with the screening procedures an additional short questionnaire containing 9 items was designed (appendix). The first three questions evaluated the burden of the two separate visits that were made as part of the screening protocol, and the psychological impact of waiting for test results. The emphasis placed on late treatment effects due to screening might be perceived as distressing, which was evaluated in question 4. The fifth question evaluated whether participants felt well informed with regard to the purpose of the screening program. The last part of the questionnaire evaluated patient satisfaction with several aspects of the screening study to assess whether participants were sufficiently prepared for the procedures of the screening tests, and were content with the aftercare. The final question evaluated satisfaction with participating in the study in general.

Statistical analysis

All statistical analysis were performed using SPSS statistical software for windows version 20 (SPSS inc., Chicago, IL). Results of the evaluation of screening questionnaire and differences between participants with and without significant CAD on CTA were analysed using the χ^2 test for trend.

The EORTC INFO-25 and QLQ-C30 questionnaires were analysed according to EORTC guidelines (22). For partially incomplete questionnaires imputation of the mean was used for scales containing at least 50% of the scores (22).

To test for significant changes in perceived information provision, fatigue or global quality of life between start and end of the screening study, results were compared using a paired *t* test. Clinical relevance of changes was defined according to published guidelines. For the EORTC INFO-25 a difference in score ≥ 10 points indicates a clinically relevant difference (23). Multivariate linear regression analysis was performed to investigate independent associations between socio-demographic, clinical characteristics and abnormalities on CTA with differences in perceived information provision, fatigue and general QoL over time. P-values of <0.05 were considered statistically significant.

Results

Patients and compliance

In the screening study, 49 patients started the screening protocol between January 2011 and March 2012. In total, 48 patients finished the screening protocol, all of whom underwent CTA. One patient did not complete the screening protocol, due to immediate intervention for severe aortic valve stenosis. Due to increased heart rates resistant to beta blocking agents and resulting in motion artefacts on CTA, 3 scans were not evaluable. In the 45 patients with evaluable CTA scans abnormalities were found in 9 patients (20%), of whom 7 needed intervention (16).

Baseline HRQL questionnaires were received from 48 patients starting the screening protocol (98%). End of study questionnaires were filled out by 43 patients (91%) finishing the study protocol (Figure 4.1). Because the 3 patients with non-evaluable

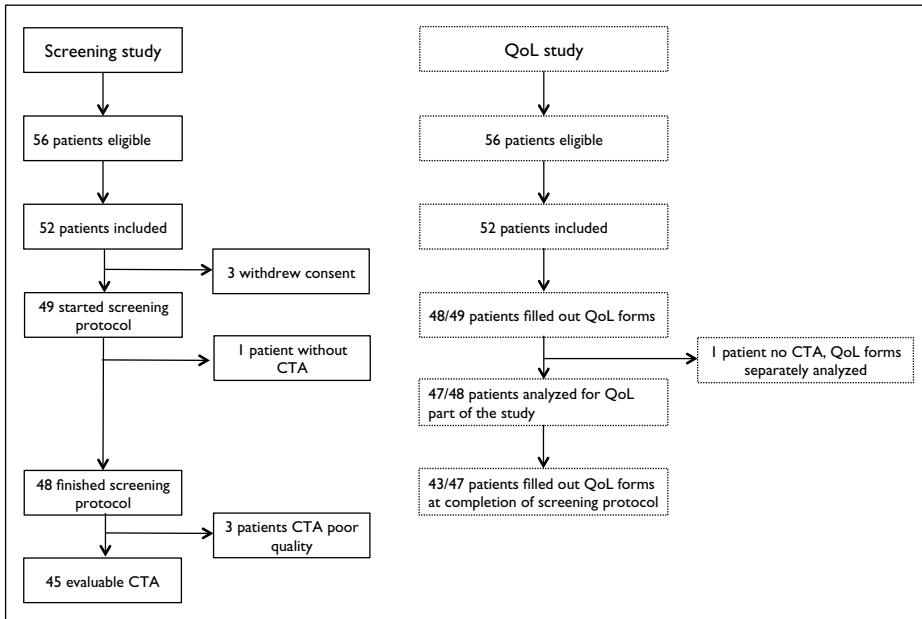


Figure 4.1: Consort diagram of screening study and quality of life study.

CTA scans did complete the entire screening protocol, they were included in the HRQL analysis. The four patients who did not return end of study questionnaires were two males and two females, all of whom had no abnormalities on CTA.

Returned questionnaires were complete for all items in 84% of the EORTC INFO-25, 99% of the EORTC QLQ-C30, 97% of the FAS and 94% of the evaluation of screening questionnaire.

Mean age of participants of the HRQL study was 47 years, mean time since diagnosis was 21 years. Most patients (70%) had been treated with combined modality treatment, and 16% had received >300 mg/m² anthracycline in their chemotherapy. Most patients (51%) had a high level of education, and 77% were currently employed (Table 4.1).

Table 4.1: Characteristics of health-related quality of life study participants

	Number of patients	%
Total	43	
Sex	Number of patients	%
Male	16	37
Female	27	63
Age and time interval	Years	Range
Median age at diagnosis HL	26	15-37
Median age at time of study	47	29-60
Median time since diagnosis	21	11-29
Stage (Ann-Arbor)	Number of patients	%
I	7	16
II	30	70
III	4	9
IV	2	5
Treatment	Number of patients	%
Median dose mediastinal radiotherapy (range)	36 (24-40)	
Number of patients receiving combined modality treatment	30	70
Number of patients receiving >300 mg/mm ² anthracycline	7	16
Marriage status	Number of patients	%
Single	3	7
Living with partner or married	36	84
Living with other family/children	4	9
Level of education	Number of patients*	%
Low	5	12
Intermediate	16	37
High	22	51
Employment status	Number of patients	%
Employed	33	77
Unemployed	6	14
Incapacitated	4	9
Cardiovascular risk factors	Number of patients	%
Current cigarette smoking	3	7
Hypertension	4	9
Diabetes mellitus	0	0
Dyslipidaemia	3	7
Family history positive for myocardial infarction	7	16
Body mass index >25	16	37

* Education levels: low = none/primary school, intermediate = lower general secondary education / vocational training, high = pre-university training / high level vocational training or university.

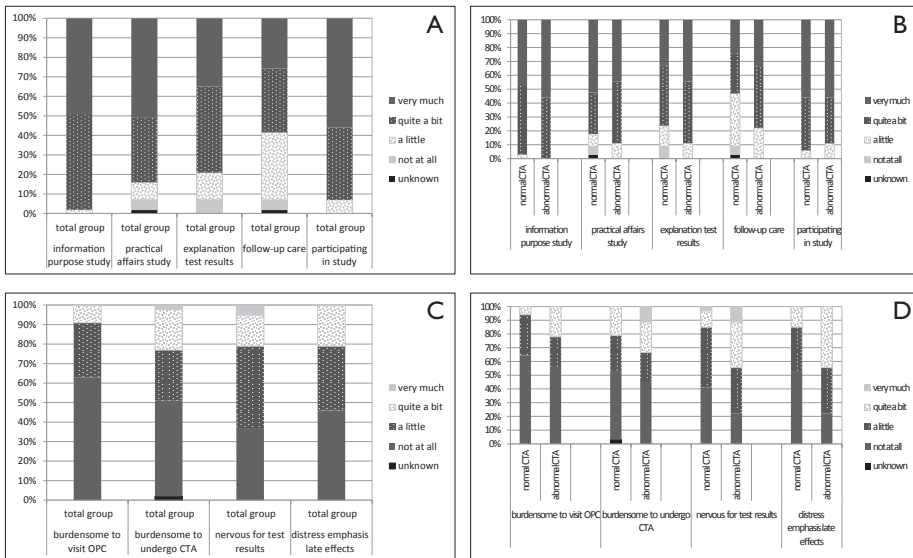


Figure 4.2: Patient responses to evaluation of screening questionnaire regarding practical aspects and perceived burden. A/B represent the results of the first five questions evaluating satisfaction with several aspects of the screening protocol, both for the total group (A) and split by group of patients with and without abnormalities on CTA (B). C/D represents the perceived burden of various aspects of the screening program, both for the total group (C) and separately for patients with and without abnormalities on CTA (D).

Evaluation of screening

Visiting the outpatient Cardiology clinic was perceived as not or a little bothersome by 91% of the participants. Undergoing CTA was perceived as bothersome by 24%, and 20% felt nervous before receiving the test results. Overall, 80% did not perceive the emphasis that was placed on possible late cardiac effects of treatment for HL by this screening study as bothersome (Figure 4.2A+C).

Patient satisfaction with participating in the screening study was high; 98% felt they were well informed about the purpose of the study, and 86% were content with the practical affairs concerning the study. Although 80% were satisfied with information and explanation of test results, 40% felt follow-up care should be improved. Overall, 93% were highly satisfied with participating in the study (Figure 4.2A+C).

Differences in the evaluation of screening questionnaire between participants with and without abnormalities on CTA were small and not statistically significant.

However, patients with abnormal CTA scans more often answered the question “how distressing is the emphasis placed on late effects” with “quite a bit” than participants with no abnormalities (44% vs 15%, $p=0.70$, Figure 4.2D).

Information provision and satisfaction, fatigue and global QoL

Results of the EORTC INFO-25 questionnaire showed that levels of information provision increased over time. Perceived levels of information concerning disease, medical tests, information on treatment and on other services such as possibilities for professional support were all significantly increased after completing the screening protocol, as compared to baseline (Figures 4.3A-D). Mean differences in scores between baseline and after screening were 19 (SD 17) points for information on disease, 40 (SD 21) points for information on medical tests and 26 (SD 15) points for information on treatment, indicating a substantial clinical relevance. Although the increase in perceived information on other services was less pronounced (from 2 to 12 points, Figure 4.3D), the difference was also clinically relevant.

Satisfaction with received information increased significantly from 20 to 48 points ($p<0.01$), a clinically relevant difference. Usefulness of given information also increased significantly, from 30 to 60 points ($p<0.01$).

There were no differences in levels of fatigue before or after the screening protocol (mean levels 21 points vs. 21 points, respectively). The number of patients indicating a substantial level of fatigue slightly increased from 13 (30%) to 15 (35%). The two new fatigue cases both had screening tests without abnormalities.

Results from the EORTC QLQ-C30 questionnaires are presented in Table 4.2. Role, physical, cognitive and emotional functioning did not change significantly over time. A small decrease in global health, from 75 points to 73 points, was found. The largest decrease was found in social functioning, from 88 points before screening to 82 points after completion, which reflects a small, clinically relevant difference.

Multivariate regression analysis did not show any significant associations between age, gender, level of education or abnormalities on CTA and perceived level of information, information satisfaction, fatigue or global health.

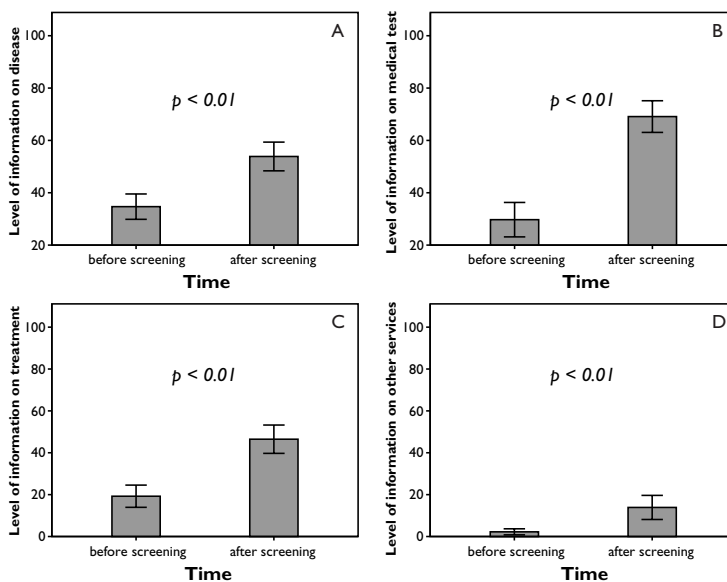


Figure 4.3: Patient responses to EORTC INFO-25 questionnaire. Mean levels of perceived information on disease (A), medical tests (B), treatment (C) and on other services (D) before start and after completing the screening program. A higher score indicates a higher level of perceived information. Error bars represent the 95% confidence intervals.

Table 4.2: Health-related quality of life and fatigue scores

	Before screening		After screening		P-value	Clinical relevance (23, 25)
	Mean	SD	Mean	SD		
QLQ C30						
<i>Functional scales</i>						
Role functioning	82	25	82	25	0.76	n.a.
Physical functioning	89	16	87	20	0.21	trivial
Cognitive functioning	84	21	82	21	0.43	trivial
Emotional functioning	81	18	82	21	0.73	trivial
Social functioning	88	20	82	27	0.03	small
Global health	76	20	72	20	0.04	small
FAS						
Total fatigue score	21.0	7.6	21.3	7.7	0.60	no

Results of the functional scale and global quality of life scores from the EORTC quality of life core questionnaire (EORTC QLQ-C30) and scores from the Fatigue Assessment Scale (FAS) both before and after screening.

Discussion

This analysis evaluated an extensive counseling and screening programme among HL survivors at risk for long-term cardiac sequelae of mediastinal radiotherapy, and assessed the effect on perceived information provision and satisfaction. Key findings of this study were that evaluation of screening was favorable, and did not differ between patients with and patients without abnormalities on the screening tests. Furthermore, perceived levels of information on disease, medical tests and treatment increased after counseling and completing the screening program, resulting in significantly improved satisfaction with information provision. Benefits of screening were felt to outweigh the burden.

Although several screening studies for radiation-induced cardiac disease have been performed, our study is the first to evaluate the psychological impact of cardiac screening on HL survivors, to assess the effect of counseling and screening on perceived information provision, and the first to evaluate HRQL both before and after screening (11-13). We showed the emphasis placed on possible late cardiac disorders due to treatment was not perceived as burdening. In fact, screening was highly valued by almost all participants in our 9-item specific questionnaire, thus indicating that perceived benefits outweigh the burden of screening, both in practical and emotional sense. Results from the validated QLQ-C30 questionnaire confirmed these results, showing no decrease in the emotional, cognitive or role functioning scales. However, counseling and screening did have a small impact on social functioning and perceived global health. We also showed that the combination of extensive information provision and screening translates into a clinically relevant improvement in perceived information and increased satisfaction with information provision. The difference found in the subscale 'information on other services' increased significantly after screening, but mean scores were still low. This could be explained by the fact that this aspect of information contains services such as information distributed on video or professional psychological support, which was not the main focus of the current study. Concerning fatigue and global quality of life, we found no significant differences between start and end of the study. This is not unexpected, considering the relatively short time interval in which the screening took place.

Eligible patients for this study were selected from the current follow-up population of HL survivors. Due to the increased risk of breast cancer prompting active screening, a large part of this population consists of females. This could explain the high percentage of female participants. Initially, almost all patients who participated in the screening protocol filled out baseline questionnaires. Compliance was high, as 91% also completed the set of questionnaires at the end of screening. The number of

missing items was limited. Therefore, the chances that the results were influenced by drop-out bias are small.

To evaluate whether the results of the cardiac tests influenced perceived information provision, fatigue or quality of life, multivariate regression analysis with a limited number of patient- and clinical variables and with CTA outcome was performed. No significant associations were found. However, the total number of patients in our analysis is small, thus limiting the possibilities for robust analysis between the two groups. Descriptive analysis of differences in evaluation of screening mostly showed similar results for patients with or without abnormalities on CTA as did satisfaction with various aspects of the screening. However, patients with abnormal CTA scans did report the emphasis placed on late effects as being burdening more often than patients without abnormalities. They also reported to be more nervous about the test results. Since the second set of questionnaires were sent out after patients finished the screening program and possible subsequent interventions, answers to both these questions could have been influenced by the result of the tests.

The role of cardiac screening in patients treated for HL is unclear. Previous screening studies have shown that prevalence of CAD detected by CTA in HL survivors is high (11, 12). Our phase II screening study did not only show a high prevalence of abnormalities on CTA in asymptomatic patients, but majority of these patients also underwent subsequent interventions.

Screening might be advisable, provided that a treatment improving outcome is available for patients with screen-detected abnormalities. Survival benefit of cardiac interventions has been demonstrated in high risk symptomatic cardiac patients (24). Whether a similar benefit can be achieved in asymptomatic HL survivors is as yet unknown. Aspects of screening such as cost-effectiveness, patient compliance and perceived burden and benefits of screening are of critical importance. Our analysis showed that the psychological impact of confrontation with possible late treatment sequelae does not seem to impede willingness to participate in screening, nor does it seem to influence satisfaction with participation.

In conclusion, in addition to a high prevalence rate of cardiac abnormalities and subsequent interventions in asymptomatic HL survivors after mediastinal radiotherapy, we have shown that the perceived burden and benefits result in a favourable patient evaluation of screening. Moreover, extensive counseling and comprehensive screening resulted in substantially increased information provision.

A positive effect of screening should be confirmed in a larger scale study. However, whether it proves to be indicated or not, screening by means of CTA and subsequent cardiac intervention is highly valued and not considered an extra psychological burden.

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Appendix: Evaluation of screening questionnaire

The following questions specifically address your visit to the Cardiology Outpatient Clinic and the CT-scan that was performed. Please answer the questions by circling the number that best applies to you. There are no 'right' or 'wrong' answers. The information that you provide will remain strictly confidential.

	Not at all	A little	Quit a bit	Very much
1) How burdensome was the visit to the Cardiology outpatient clinic for you?	1	2	3	4
2) How burdensome was it for you to undergo the CT scan?	1	2	3	4
3) How nervous were you about receiving the test results?	1	2	3	4
4) How distressing is the emphasis that is placed on possible late side effects of your treatment to you?	1	2	3	4
How satisfied are you with:	Not at all	A little	Quit a bit	Very much
5) the information that was given to you concerning the purpose of this screening study?	1	2	3	4
6) the explanation given to you concerning the practical affairs of this screening study?	1	2	3	4
7) the explanation given to you concerning all test results?	1	2	3	4
8) the follow-up care after finishing all tests?	1	2	3	4
9) participating in this study?	1	2	3	4