

# International Cross-cultural Field Validation of an EORTC questionnaire module for patients with primary liver cancer, HCC18

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Progress report, March 2009  
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# Collaborators

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## ■ Co-investigators

- Jane M Blazeby, Philip J Johnson, Anna Costantini (Italy), Ludovic Trinquart (France), Benny Zee, Ronnie T. Poon (Hong Kong), Heng-Chia Chiu, PhD (Taiwan), Naoko Mikoshiba (Japan), Chonghua Wan (China)
- Newcomers: Nigel Heaton (UK), Ludovic Trinquart (France)

## ■ Statistician

- Chin-Fu Hsiao, PhD, Data management centre: Division of Biostatistics and Bioinformatics, National Health Research Institutes, Taiwan



# Aims of the project

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- The objective of this study is to
  - test the reliability, clinical and psychometric validity of the EORTC QLQ-HCC18
  - in an international sample of patients with primary liver cancer (hepatocellular carcinoma, HCC).



# Groups of patients

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- **A:** hepatectomy or other surgeries (including transplant, etc.)
- **B:** any kind of ablation (radiofrequency, ethanol, etc.) alone
- **C:** any kind of embolisation (lipiodol, chemo- etc.) alone
- **D:** systemic therapy alone
- **E:** off-treatment for at least 12 months



# Timing of assessment

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- First assessment
  - **A, B, C, D:** before treatment
  - **E:** after completion of any treatment for at least 12 months without evidence of recurrence
- Second assessment
  - **A:** at three months (range: 12-15 weeks) after surgery
  - **B:** at one month (range: 4-6 weeks) after ablation
  - **C:** at one month (range: 4-6 weeks) after embolisation
  - **D:** at one week (range: 7-10 days) of completion of systemic therapy
  - **E:** re-test one week later



# Required clinical evaluations

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- Major Measurement Instruments
  - the EORTC QLQ-C30 (version 3.0)
  - the primary liver cancer module (QLQ-HCC18)
- Debriefing questionnaire
  - the time taken to complete the QLQ-C30 and QLQ-HCC18
  - the need for help in completing the questionnaires
  - querying whether any of the items were confusing; difficult to answer or upsetting, suggestions of re-wording, etc.
- Case Report Form



# Forms to return

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- First assessment
  - Forms 1 & 2
  - Questionnaires
  - Patient debriefing (Forms 4)
- Second assessment
  - Forms 3 & 5
  - Questionnaires
  - Off-study form (missing questionnaires)



# Schedule and budgets

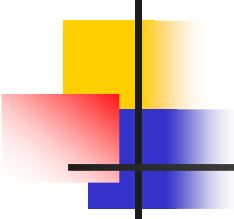
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- Two years
  - From November 2007
  - To October 2009
- Total budget: Euro 48500
  - Interview fee 12500 paid directly to co-PIs by the EORTC
  - Other expenses 36000 paid to NTU (PI)
- Newsletter: monthly since August 2008

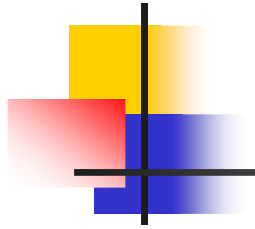
**Table 1 Patients registered and CRFs received in data centre**

Hospital	Register	# of CRFs in Statistical Center					Total
		Group A	Group B	Group C	Group D	Group E	
National Taiwan University Hospital, Taiwan	42	11	5	10	5	11	42
Kaohsiung Medical University, Taiwan	50	30	0	20	0	0	50
United Bristol Healthcare Trust, UK	5	0	0	0	0	0	0
Sant'Andrea Hospital 2nd Faculty of Medicine Sapienza University of Rome, Italy	2	0	0	0	0	0	0
Queen Mary Hospital, HK	47	4	10	0	0	10	24
<b>Total</b>	<b>146</b>	<b>45</b>	<b>15</b>	<b>30</b>	<b>5</b>	<b>21</b>	<b>116</b>

**Table 2 Demographic characteristics**



	Total (N=116)
<b>Age</b>	53.12± 11.71
<b>Gender</b>	
Male	94 ( 81.03%)
Female	22 ( 18.97%)
<b>Race</b>	
(Ethnic) Chinese	116 (100.00%)
<b>Highest level of education completed</b>	
less than compulsory school education	34 ( 29.31%)
compulsory school education	29 ( 25.00%)
post compulsory school education below university level	29 ( 25.00%)
university level or above	24 ( 20.69%)

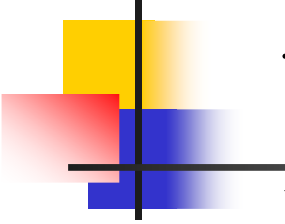


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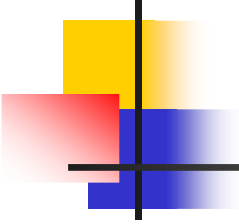
	Total (N=116)
<b>Employment status</b>	
employed full time (could be on sick level)	45 ( 38.79%)
homemaker	11 ( 9.48%)
student	2 ( 1.72%)
unemployed	14 ( 12.07%)
retired	38 ( 32.76%)
self-employed	5 ( 4.31%)
other	1 ( 0.86%)
<b>Marital status</b>	
single	8 ( 6.90%)
married or living with partner	100 ( 86.21%)
separated, divorced, widow(er)	8 ( 6.90%)
<b>Cohabitants</b>	
alone	7 ( 6.03%)
with family	108 ( 93.10%)
with other adults	1 ( 0.86%)

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**Table 3 Basic clinical information**



	Total (N=116)
<b>Diagnosis of HCC</b>	
surveillance scan	92 ( 79.31%)
surveillance afp	2 ( 1.72%)
clinical diagnosis	11 ( 9.48%)
incidental finding	9 ( 7.76%)
other	2 ( 1.72%)
<b>Histologically diagnosed</b>	
yes	100 ( 86.21%)
no	16 ( 13.79%)
<b>Tumor number</b>	
single	86 ( 74.14%)
multiple	30 ( 25.86%)



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**Total**  
**(N=116)**

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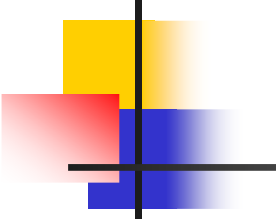
**Tumor involvement**

within one lobe	102 ( 87.93%)
more than one lobe	10 ( 8.62%)
invading adjacent organs	2 ( 1.72%)
metastatic	2 ( 1.72%)

**Cirrhosis**

no	34 ( 29.31%)
unknown	5 ( 4.31%)
yes, specify:	77 ( 66.38%)
Hepatitis B	55 ( 71.43%)
Hepatitis C	23 ( 29.87%)
Alcohol related	2 ( 2.60%)
other	1 ( 1.30%)

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Total  
(N=116)

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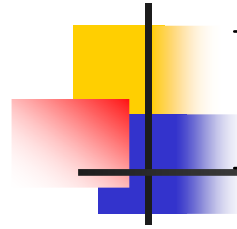
**Comorbid disease**

Hypertension	28 ( 24.14%)
Diabetes	26 ( 22.41%)
Renal	7 ( 6.03%)
Rheumatic	1 ( 0.86%)
Cardiovascular	8 ( 6.90%)
Respiratory	2 ( 1.72%)
other	14 ( 12.07%)

**Karnosky score**

=100	63 ( 54.31%)
<100	53 ( 45.69%)

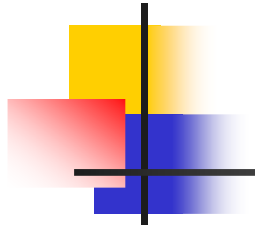
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	Total (N=116)
<b>Clinical significant portal hypertension</b>	
yes	5 ( 4.31%)
<b>Child-Pugh grade for HCC</b>	
A	105 ( 90.52%)
<b>Bilirubin</b>	
Abnormal ( > 2 mg /dl)	31 ( 26.72%)
<b>α-FP</b>	
abnormal ( > 20 ng / ml)	47 ( 40.52%)

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**Past treatment history**

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**Surgery**

Hepatectomy	60 ( 51.72%)
Other	5 ( 4.31%)

**Ablation**

Radiofrequency	4 ( 3.45%)
Ethanol	1 ( 0.86%)
Other	2 ( 1.72%)

**Embolisation**

Chemo	51 ( 43.97%)
Lipiodol	16 ( 13.79%)
Other	2 ( 1.72%)

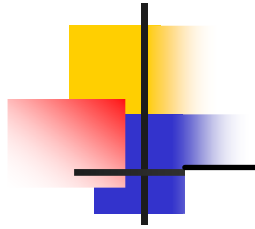
**Systemic therapy**

6 ( 5.17%)

**No treatment history**

22 ( 18.97%)

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**Table 4a Test-retest for group E (multi-item scales)**

	Between subject S.D.	Within subject S.D.	ICC
Fatigue	0.46	0.26	0.76
Jaundice	0.61	0.20	0.90
Nutrition	0.43	0.15	0.90
Pain	0.53	0.33	0.72
Fever	0.44	0.24	0.76
Body image	0.53	0.28	0.79

**Table 4b Test-retest for group E (single-item scales)**

Items	Absolute score difference				Missing	Simple Kappa	Weighted Kappa
	0	1	2	3			
Thirsty	14	7	0	0	0	0.46	0.52
Abdominal swelling	14	7	0	0	0	0.33	0.40
Sex interest	18	3	0	0	0	0.70	0.79

**Table 5 Internal consistency, item convergent and discriminant validity for 1st HCC18 (Overall, N=116)**

<b>Scales (no. of items)</b>	<b>Cronbach's <math>\alpha</math></b>	<b>Item - own scale correlation</b>	<b>Item - other scale correlation</b>	<b>Scaling error</b>
Fatigue (3)	0.56	0.22 - 0.54	0.15 - 0.53	0/24
Nutrition (5)*	0.68	0.32 - 0.54	-0.11 - 0.83	1/40
Jaundice (2)	0.46	0.31	0.17 - 0.52	0/16
Pain (2)	0.44	0.28	0.05 - 0.50	0/16
Fever (2)	0.48	0.32	-0.02 - 0.39	0/16
<b>Body image (2)*</b>	<b>0.10</b>	<b>0.05</b>	<b>-0.11 - 0.72</b>	<b>6/16</b>
Thirsty (1)			0.15 - 0.33	
Abdominal swelling (1)			0.08 - 0.43	
Sexual interest (1)			0.02 - 0.35	

\* One item overlaps.



# Items with scaling error

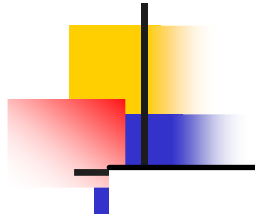
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- Nutrition
  - Q3 (lost muscle): with Body image
- Body image
  - Q3 (lost muscle): with Fatigue, Nutrition, and Pain
  - Q5 (appearance of abdomen): with Fatigue, Jaundice, and Pain

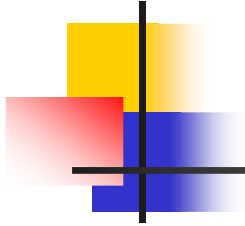
**Table 6 Known-groups comparisons (only significant results)  
(higher score means severer symptoms and poorer QOL)**

	Single tumor (n=86)		Multiple tumor (n=30)		P-value of F-test	P-value of KW-test
	Mean (S.D.)	Median (Min, Max)	Mean (S.D.)	Median (Min, Max)		
Abdominal swelling	10.1± 19.8	0.00(0.00, 100)	22.2± 25.3	33.3(0.00, 100)	0.0084	0.0040

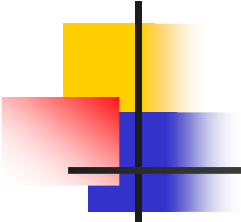
	No cirrhosis or unknown (n=77)		Cirrhosis (n=39)		P-value of F-test	P-value of KW-test
	Mean (S.D.)	Median (Min, Max)	Mean (S.D.)	Median (Min, Max)		
Jaundice	16.5± 19.8	16.7(0.00,66.7)	8.12± 13.7	0.00(0.00,50.0)	0.0201	0.0175



	Bilirubin < 2 (n=85)		Bilirubin ≥ 2 (n=31)		P-value of F-test	P-value of KW-test
	Mean (S.D.)	Median (Min, Max)	Mean (S.D.)	Median (Min, Max)		
Fatigue	15.6± 15.7	11.1(0.00,77.8)	24.4± 17.5	22.2(0.00,66.7)	0.0109	0.0095
Jaundice	10.2± 15.9	0.00(0.00,66.7)	23.1± 21.4	16.7(0.00,66.7)	0.0006	0.0007
Pain	12.2± 16.9	0.00(0.00,83.3)	17.7± 15.5	16.7(0.00,50.0)	0.1109	0.0330
Sexual interest	7.84± 20.3	0.00(0.00, 100)	22.6± 32.6	0.00(0.00, 100)	0.0044	0.0035



- Responsiveness:
  - failed to show significant differences before and after treatment
  - in all patients of groups A through D
  - Between groups A, B+C (too few Ds)
- Patients' debriefing
  - Q37 itching: difficult to understand or confusing
  - Q38 shoulder pain: one co-PI rated as confusing
  - Time consumed and help (see the following table)



**Table 7 - Patient debriefing**

	Total (N=116)
How long did it take to complete C30 & HCC18	
less than 10 min.	84 ( 72.41%)
between 10 and 30 min.	29 ( 25.00%)
more than 30 min.	3 ( 2.59%)
Did any one help patient to complete	
No	45 ( 38.79%)
Yes	71 ( 61.21%)



# Major problems / challenges

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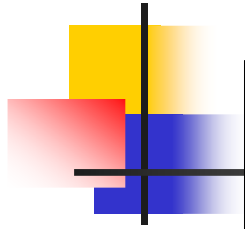
- Slow recruitment from European countries and one centre in HK
  - Please hurry up! ~~~
  - More centres from Europe (France, ...)
  - An extended project may be needed!
- Imbalance among groups
  - A C E > B D, few B in Asian countries
  - may be solved after Japan joins us (esp. for group B)
- Timing of 2nd assessment may be too late to demonstrate treatment complications
  - To be included in Discussion



# Extended Project

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- Background
  - New development of targeted therapies (sorafenib, ...)
  - Slow recruitment
- To extend the ongoing phase IV validation of this module
  - to recruit enough patients and
  - to add a subgroup in group D (systemic therapy) for patients undergoing targeted therapy.



<b>TOTAL EXTENDED PROJECT (12 MONTHS)</b>	<b>EUROS</b>
Master level research assistant 100% FTE for 12 months (Taiwan salary level, plus labour and health insurance, and superannuation) +25% overhead	16000
Temporary Workers + 25% overhead	500
Travel/Expenses to two EORTC QLG Meetings + 25% overhead	3000
Miscellaneous Expenses + 25% overhead	500
Total	20000