Gestational Trophoblastic Neoplasia

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STAGING

In 2000 FIGO recommended a clinical staging of gestational trophoblastic tumors and requested that such cases should be reported to the Annual Report on the Results of Treatment in Gynecological Cancer. For this purpose the definitions of the clinical stages of gestational trophoblastic tumors are presented in Table 1.

According to FIGO, hydatidiform mole should be registered but not be staged as Stage 0 because if hCG persists and the patient requires chemotherapy restaging would be required. Such restaging transgresses the basic principle of any staging system. Patients with hydatidiform mole are placed on record but staging only applies to trophoblastic neoplasia.

Cases which do not fulfill the criteria for any given stage should be listed separately as unstaged. It should be realized that most cases of low risk metastatic disease are comprised by Stage III, while the high risk group of metastatic tumors first described by Hammond is the group that comes under Stage IV.

In 2000 FIGO accepted the World Health Organization scoring system based on prognostic factors that were first devised by Prof. Kenneth Bagshawe. The score values for the risk factors will be 1, 2 and 4. Blood groups will not be used in the scoring system. Liver metastases will be given a score of 4. The cut-off score for low-risk and high-risk neoplasia was ratified by the June 2002 FIGO Committee on Gynecologic Oncology announcement. A score of 6 or less is low risk disease treatable by single agent chemotherapy. A score of 7 or greater is high risk disease that requires combination chemotherapy. Medium risk disease has been eliminated.

This combining of the modified WHO risk factor scoring system with the FIGO staging was accepted by the FIGO Committee on Gynecologic Oncology in September 2000 and ratified in June 2002 with the FIGO announcement. It is now part of the FIGO staging and scoring system for gestational trophoblastic neoplasia.

Table 1
GTN: FIGO staging and classification (Washington, 2000[a])

FIGO Anatomical Staging

Stage I	Disease confined to the uterus
Stage II	GTN extends outside of the uterus, but is limited to the genital structures (adnexa, vagina, broad ligament)
Stage III	GTN extends to the lungs, with or without known genital tract involvement
Stage IV	All other metastatic sites

Modified WHO Prognostic Scoring System as Adapted by FIGO

Scores	0	1	2	4
Age	<40	⩾40	–	–
Antecedent pregnancy	mole	abortion	term	–
Interval months from index pregnancy	<4	4–6	7–12	>12
Pretreatment serum hCG (iu/l)	$<10^3$	10^3–10^4	10^4–10^5	$>10^5$
Largest tumor size (including uterus)	<3	3–4 cm	⩾5 cm	–
Site of metastases	lung	spleen, kidney	gastro-intestinal	liver, brain
Number of metastases	–	1–4	5–8	>8
Previous failed chemotherapy	–	–	single drug	2 or more drugs

[a] Ngan HYS, Bender H, Benedet JL, Jones H, Montruccoli GC, Pecorelli S. Gestational Trophoblastic Neoplasia, FIGO 2000 staging and classification. Int. J. Gynecol. Obstet. 2003; 83: 175–77.

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Table 2
GTN: Stage grouping for GTN

FIGO stage	UICC		
	T	N	Risk factors
Ia	T1a	M0	None
Ib	T1b	M0	One
Ic	T1c	M0	Two
IIa	T2a	M0	None
IIb	T2b	M0	One
IIc	T2c	M0	Two
IIIa	Any T	M1a	None
IIIb	Any T	M1a	One
IIIc	Any T	M1a	Two
IVa	Any T	M1b	None
IVb	Any T	M1b	One
IVc	Any T	M1b	Two

Following are the criteria to diagnose gestational trophoblastic neoplasia:

(1) At least 4 values of persistently elevated hCG plateau (days 1, 7, 14 and 21) or longer or sequential rise of hCG for two weeks (days 1, 7, 14) or longer. The actual values of hCG are left to the discretion of individual physicians.
(2) Lung metastases are diagnosed by chest x-ray.

Rules for classification

In order to stage and allot a risk factor score, a patient's diagnosis is allocated to a stage as represented by a Roman numeral I, II, III, and IV. This is then separated by a colon from the sum of all the actual risk factor scores expressed in Arabic numerals, e.g. Stage II:4, Stage IV:9. This stage and score will be allotted for each patient.

DEFINITIONS OF TREATMENTS

Treatment definitions are given in Table 4.

Table 3
GTN: FIGO nomenclature (Singapore 1991) **(no longer adopted for FIGO classification)**

Stage I	Disease confined to the uterus
Ia	Disease confined to the uterus with no risk factors
Ib	Disease confined to the uterus with one risk factor
Ic	Disease confined to the uterus with two risk factors
Stage II	GTD extends outside of the uterus, but is limited to the genital structures (adnexa, vagina, broad ligament)
IIa	GTD involving genital structures without risk factors
IIb	GTD extends outside of the uterus, but is limited to genital structures with one risk factor
IIc	GTD extends outside of the uterus, but is limited to the genital structures with two risk factors
Stage III	GTD extends to the lungs, with or without known genital tract involvement
IIIa	GTD extends to the lungs, with or without genital tract involvement and with no risk factors
IIIb	GTD extends to the lungs, with or without genital tract involvement and with one risk factor
IIIc	GTD extends to the lungs, with or without genital tract involvement and with two risk factors
Stage IV	All other metastatic sites
IVa	All other metastatic sites, without risk factors
IVb	All other metastatic sites, with one risk factor
IVc	All other metastatic sites, with two risk factors

Table 4
GTN: Definitions of treatments

Treatment	Definition
None	No treatment.
Chemotherapy	Performed either as a prophylactic treatment or as primary treatment following D&C with residual disease (uterine or extrauterine).
Surgery alone	Only hysterectomy (because of GTN), with normalization of serum β-hCG levels, performed on patients who did not undergo chemotherapy before and/or after hysterectomy.
Chemotherapy + surgery	Chemotherapy plus surgery (abdominal and/or pelvic surgery, craniotomy, lobectomy of the lung, etc.) with the intention to treat GTN. Please note that chemotherapy can be given before and/or after surgery.

DATA ANALYSIS

Summary and comments

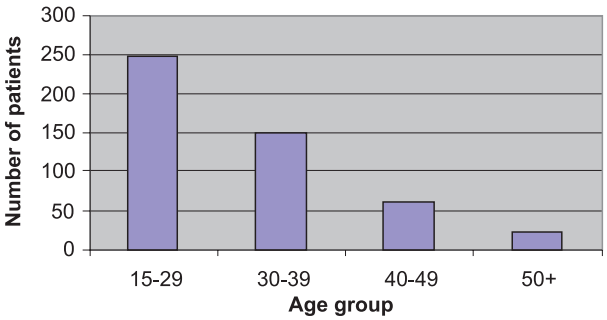
The staging system for GTN was revised in 2000 and officially published in 2002[a]. The current staging system no longer includes substages and adopts a modified prognostic risk-factor scoring system. This new staging system was used for data collection and analysis for the present volume of the Annual Report. We are now able to identify outcomes by risk grouping and stage. In the future, a larger more complete data base, with combined stage and individual risk factor scores will permit more detailed data analysis.

Although the current staging system has retained 8 specific risk factors, there still remains the need for further refinement using multivariate analysis as to further identify which factors are truly independent prognostically.

The total number of GTN cases continues to drop from 1938 in Vol. 20 (1979–1981) to 483 in the current volume (1999–2001). This decrease has occurred even though the total number of contributing centers has increased. The exact reasons for this change are not apparent; factors such as decreased parity, more frequent use of ultrasound in early pregnancy and improved socio-economic conditions in many countries may be responsible. Other reasons may be the application of more stringent criteria to the diagnosis of GTNs reported in the 2000 Gynecologic Oncology Report and the exclusion of molar pregnancy with normal regression patterns of hCG from GTN.

It may be helpful to consider having a separate registry on molar pregnancy (including partial and complete moles) to better determine the percentage of GTN developing from molar pregnancy. This would also avoid duplicate entries for a patient with a molar pregnancy, the so-called Stage 0, who post-evacuation develops a GTN Stage I:3 requiring chemotherapy. This would avoid the potential problem of mixing benign conditions, e.g. moles, with malignant GTN.

Data analysis indicates that GTN is a disease of reproductive age group women with the highest percentage of cases occurring between ages of 25 and 29 years. Approximately 80% of patients are younger than 40. These data underscore the need to identify and treat such patients promptly with the appropriate chemotherapy not only to reduce mortality but also to preserve reproductive function if desired. According to simple anatomical staging, the majority of GTN cases were Stage I and the majority of these cases were treated with chemotherapy. It is hence not surprising to have a 97.3% overall 5-year survival estimate. It is interesting to note that using FIGO scoring to divide patients into low- and high-risk groups based on a cut-off of 6 shows the same survival in the low-risk group as in Stage I. However, for Stage IV disease, despite multiple modalities of treatment, the 5-year survival estimate is only 62%. For the FIGO high-risk group using 6 as cut-off, the 5-year survival estimate is 79.5%, which is less discriminatory when compared to staging where Stage II and III show 83–86% 5-year survival compared to Stage IV. Attempting to re-group the scoring to 3 groups as low risk (0–6), intermediate (7–12) and high risk (>12) seems more discriminatory. The intermediate-risk group has a 5-year survival estimate of 84% which is similar to that of Stage II and III, while in the high-risk group the survival estimate is 68%.



Age group	Patients (*n*)	Percentage (%)
15–29	249	51.6
30–39	150	31.1
40–49	61	12.6
50+	22	4.6
Total	483	100.0

Fig. 1. GTN: patients treated in 1999–2001. Distribution by age group.

As mentioned above, with more data accumulated, it would be interesting to perform further analyses such as by grouping stage and score together to form subgroups; to use different cut-off scores to determine the best cut-off, to form either 2 risk groups or 3 risk groups, or to modify the risk factors by different weighting or inclusion or exclusion.

It is important to bear in mind that we can make a diagnosis of early-stage GTN by monitoring patients after molar pregnancy where early diagnosis and treatment ensured a survival rate of almost 100%. On the other

[a] FIGO staging for gestational trophoblastic neoplasia 2000. FIGO Committee on Gynecologic Oncology. Int J Gynaecol Obstet 2002 Jun; 77(3): 285–7.

hand, a high index of suspicion is required in women in reproductive age presenting with pulmonary and cerebral symptoms. The reported results indicate that this is a disease that responds well to appropriate chemotherapy. Prompt diagnosis and early referral to experienced centers will ensure optimum outcomes for patients with advanced-stage disease and those with high-risk features (62–86% 5-year survival). Referral to an experienced center could ensure better outcome especially in patients with Stage II and above or those in a high-risk group.

Table 5
GTN: patients treated in 1999–2001. Distribution of patients by center and stage

		All	Not available	Stage I	Stage II	Stage III	Stage IV
All centers		483	66	328	12	51	26
South Africa	Cape Town (L van Wijk)	18	–	13	–	–	5
	Pretoria (G Lindeque)	12	7	3	–	2	–
Argentina	Buenos Aires (J Sardi)	1	–	–	–	–	1
	Buenos Aires (R Testa)	1	–	1	–	–	–
	Santa Fe (A Ellena)	7	–	6	–	1	–
Brazil	Porto Alegre (E MH Uberti)	39	–	32	2	5	–
Peru	Arequipa (L Medina Fernandez)	25	–	24	–	1	–
USA	Boston, MA (RS Berkowitz)	23	–	15	–	7	1
	New Haven, CT (EI Kohorn)	8	1	4	1	1	1
China	Hong Kong (HYS Ngan)	27	1	21	–	3	2
India	Bangalore (U Devi)	16	–	12	1	2	1
	Calicut (PK Sekharan)	41	–	40	1	–	–
Japan	Fukuoka (N Tsukamoto)	1	–	1	–	–	–
	Gunma (T Kanuma)	8	–	6	–	2	–
	Kumamoto (H Katabuchi)	12	–	7	–	3	2
	Niigata (Y Aoki)	19	–	18	–	–	1
Korea	Kyunggi-do (SJ Kim)	12	–	8	1	2	1
	Seoul (HP Lee)	6	–	2	–	3	1
	Seoul (JE Mok)	7	–	6	–	1	–
	Seoul (H-S Saw)	4	–	–	1	3	–
Thailand	Bangkok (S Wilailak)	12	–	10	1	–	1
	Songkhla (V Wootipoom)	30	–	16	1	10	3
Pakistan	Islamabad (R Shaheen)	1	–	–	–	1	–
Austria	Graz (M Lahousen)	4	–	4	–	–	–
	Innsbruck (C Marth)	4	–	4	–	–	–
Croatia	Zagreb (S Jukic)	23	–	23	–	–	–
Finland	Oys (P Vuolo-Merilä)	4	–	4	–	–	–
France	Bordeaux (ML Campo)	5	–	2	–	–	3
Germany	Greifswald (G Koehler)	2	–	1	1	–	
	Hannover (H Kühnle)	1	–	–	–	–	1
Italy	Brescia (S Pecorelli)	4	–	3	–	–	1
Netherlands	Amsterdam (MPM Burger)	13	–	13	–	–	
Portugal	Coimbra (O Campos)	21	–	20	–	–	1
	Coimbra (C Freire de Oliveira)	6	–	5	1	–	
Spain	Las Palmas de Gran Canaria (O Falcon-Vizcaino)	47	47	–	–	–	–
	Madrid (A de Armas Serra)	5	–	4	–	–	1
Sweden	Gothenburg (G Horvath)	8	8	–	–	–	–
	Örebro (B Sorbe)	4	–	2	–	2	–
Ukraine	Odessa (A Zelinsky)	7	–	2	2	3	–
UK	Cambridge (LT Tan)	3	3	–	–	–	–

Table 6
GTN: patients treated in 1999–2001. Distribution of patients (%) by country and mode of treatment (Stage I), $n = 328$

Country	Number of patients	First line of treatment (%)				
		None	CT	Surgery alone	CT + surgery	Other
All	328	16	59	10	9	3
South Africa	16	–	69	6	25	–
Argentina	7	–	14	–	–	–
Brazil	32	–	97	–	–	3
Peru	24	–	4	96	–	–
USA	15	7	87	–	7	–
China	21	–	90	–	5	5
India	52	–	90	–	10	–
Japan	32	47	34	6	9	–
Korea	16	–	88	–	13	–
Thailand	26	–	81	–	19	–
Austria	8	–	–	–	–	100
Croatia	23	74	9	9	9	–
Finland	4	–	100	–	–	–
France	2	–	100	–	–	–
Germany	1	–	–	100	–	–
Italy	3	–	–	33	33	33
Netherlands	13	31	62	8	–	–
Portugal	25	68	16	–	12	–
Spain	4	–	75	–	25	–
Sweden	2	–	100	–	–	–
Ukraine	2	–	50	50	–	–

Table 7
GTN: patients treated in 1999–2001. Distribution of patients (%) by country and mode of treatment (Stage II), $n = 12$

Country	Number of patients	First line of treatment (%)				
		None	CT	Surgery alone	CT + surgery	Other
All	12	–	33	8	42	17
Brazil	2	–	–	–	–	100
India	2	–	100	–	–	–
Korea	2	–	100	–	–	–
Thailand	2	–	–	–	100	–
Germany	1	–	–	–	100	–
Portugal	1	–	–	–	100	–
Ukraine	2	–	–	50	50	–

Table 8
GTN: patients treated in 1999–2001. Distribution of patients (%) by country and mode of treatment (Stage III), $n = 51$

Country	Number of patients	First line of treatment (%)				
		None	CT	Surgery alone	CT + surgery	Other
All	51	2	71	–	27	–
South Africa	2	50	50	–	–	–
Argentina	1	–	100	–	–	–
Brazil	5	–	80	–	20	–
Peru	1	–	100	–	–	–
USA	7	–	71	–	29	–
China	3	–	100	–	–	–
India	2	–	100	–	–	–
Japan	5	–	80	–	20	–
Korea	9	–	56	–	44	–
Thailand	10	–	70	–	30	–
Pakistan	1	–	100	–	–	–
Sweden	2	–	50	–	50	–
Ukraine	3	–	33	–	67	–

Table 9
GTN: patients treated in 1999–2001. Distribution of patients (%) by country and mode of treatment (Stage IV), $n = 26$

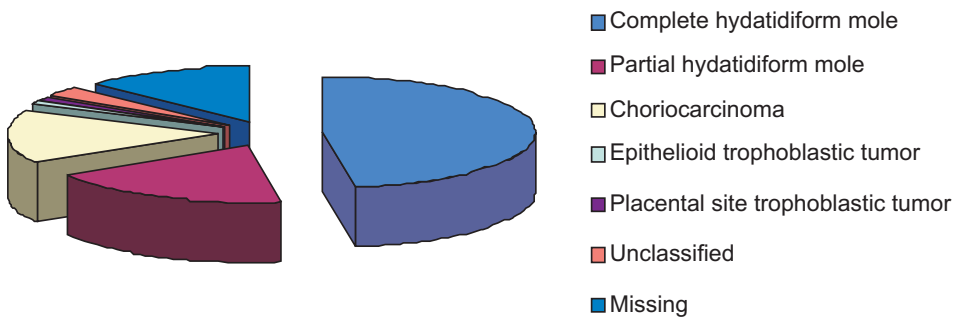
Country	Number of patients	First line of treatment (%)				
		None	CT	Surgery alone	CT + surgery	Other
All	26	–	38	–	46	15
South Africa	5	–	20	–	80	–
Argentina	1	–	–	–	100	–
USA	1	–	–	–	–	100
China	2	–	50	–	–	50
India	1	–	–	–	–	100
Japan	3	–	–	–	67	33
Korea	2	–	50	–	50	–
Thailand	4	–	50	–	50	–
France	3	–	100	–	–	–
Germany	1	–	–	–	100	–
Italy	1	–	100	–	–	–
Portugal	1	–	–	–	100	–
Spain	1	–	100	–	–	–

Table 10
GTN: patients treated in 1999–2001. Distribution of patients by mode of treatment and FIGO stage

Treatment	All	%	Missing	I	II	III	IV
No treatment	97	20.1	42	54	–	1	–
CT	252	52.2	7	195	4	36	10
Surgery alone	42	8.7	9	32	1	–	–
CT+ surgery	61	12.6	2	28	5	14	12
Other non-standard	19	3.9	2	11	2	–	4
Missing	12	2.5	4	8	–	–	–
All	483	100.0	66	328	12	51	26

Table 11
GTN: patients treated in 1999–2001. Distribution of patients by mode of treatment and histologic type

Treatment	Complete hydatidiform mole	Partial hydatidiform mole	Chorio-carcinoma	Epithelioid trophoblastic tumor	Placental site trophoblastic tumor	Unclassified	Missing
No treatment	28	67	–	–	1	–	1
CT	142	14	39	2	–	7	48
Surgery alone	29	2	6	1	1	–	3
CT+ surgery	20	1	27	–	4	5	4
Other non-standard	7	5	2	1	1	1	2
Missing	3	2	2	–	–	–	5
All	229	91	76	4	7	13	63

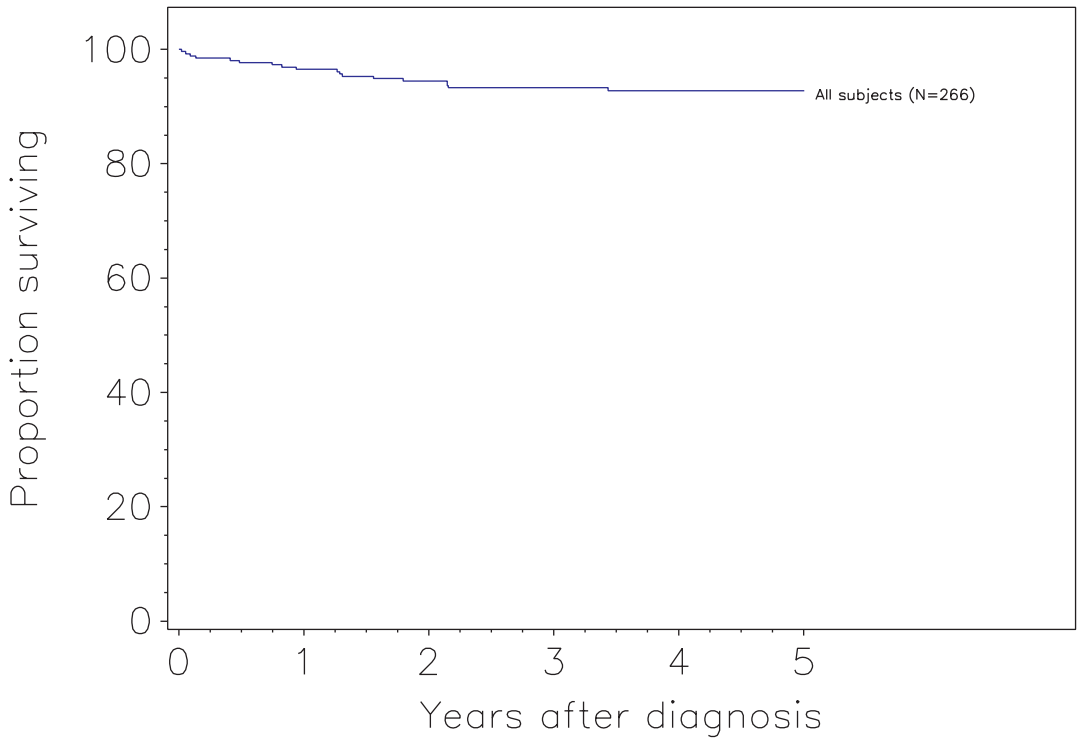


Histotype	All	%	Missing	I	II	III	IV
Complete hydatidiform mole	229	47.4	26	181	5	14	3
Partial hydatidiform mole	91	18.8	32	58	–	1	–
Choriocarcinoma	76	15.7	4	35	4	19	14
Epithelioid trophoblastic tumor	4	0.8	1	2	–	1	–
Placental site trophoblastic tumor	7	1.4	–	4	1	–	2
Unclassified	13	2.7	–	7	–	3	3
Missing	63	13.0	3	41	2	13	4
All	483	100.0	66	328	12	51	26

Fig. 2. GTN: patients treated in 1999–2001. Histopathology by FIGO stage.

Table 12
GTN: patients treated in 1999–2001. Response to treatment by FIGO stage

Response	All	Missing	Stage I	Stage II	Stage III	Stage IV
Missing	44	12	32	–	–	–
Complete response	383	49	264	9	43	18
Partial response	13	–	6	1	3	3
Stable disease	1	–	–	–	–	1
Progressive disease	8	2	1	–	2	3
Not assessable	34	3	25	2	3	1



	Patients (*n*)	Mean age (yr)	Overall survival (%) at				
			1 year	2 years	3 years	4 years	5 years
All subjects	266	32.2	96.5	94.5	93.2	92.7	92.7

Fig. 3. GTN: patients treated in 1999–2001. Overall survival, $n = 266$.

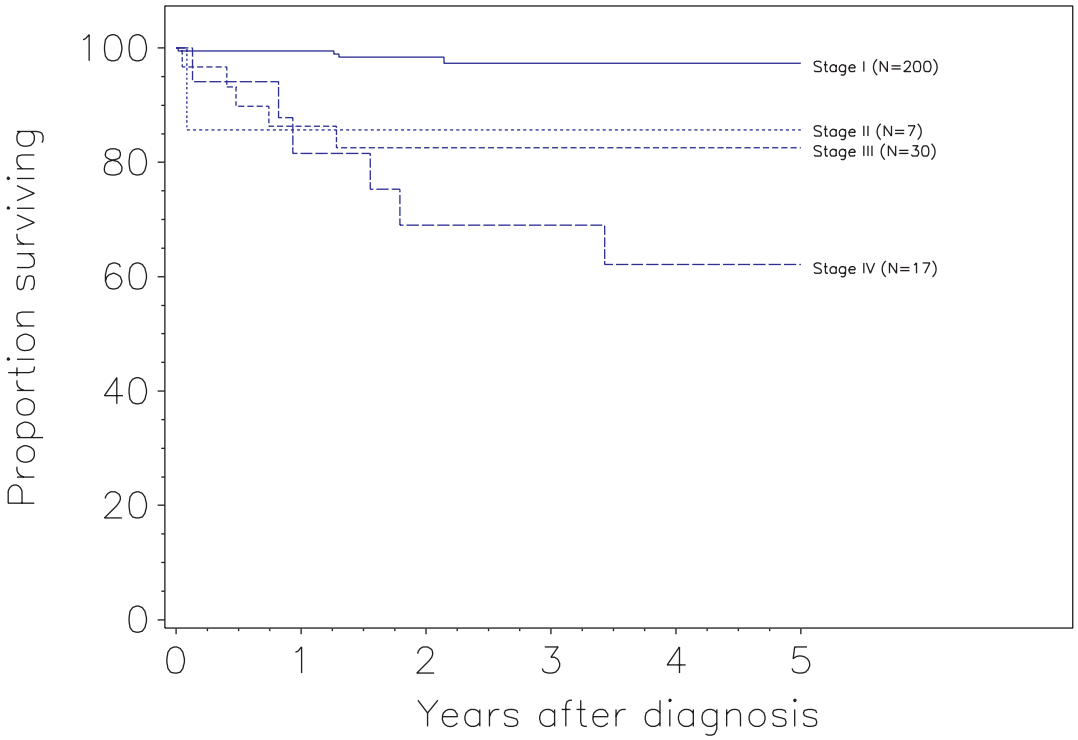
Table 13
GTN: Review of the data collection of Volumes 19–26

Vol.	Year	Patients (*n*)	Contributing centers
19	1976–78	1688[a]	21
20	1979–81	1938[a]	22
21	1982–86	996[a]	24
22	1987–89	408	15
23	1990–92	234	22
24	1993–95	411	31
25	1996–98	901	39
26	**1999–2001**	**483**	**39**
Total		**7059**	

[a] These figures include cases that had been collected in wider time intervals compared with the period of data collection of those volumes, or that might be already present in the data reported in previous volumes.

Table 14
GTN: patients treated in 1999–2001. Distribution by FIGO stage

FIGO stage	Patients (*n*)	Percentage (%)
I	328	67.9
II	12	2.5
III	51	10.6
IV	26	5.4
Missing	66	13.7
All	483	100.0



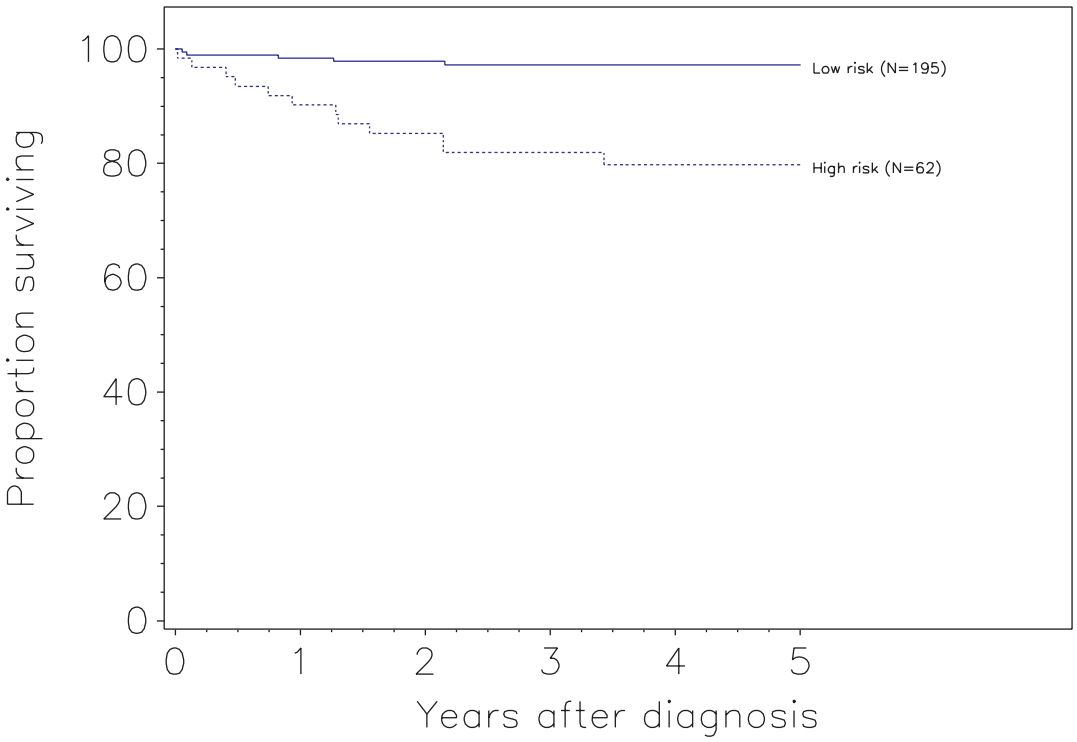
Stage	Patients (*n*)	Mean age (yr)	Overall survival (%) at					Hazards ratio[a] (95% CI)
			1 year	2 years	3 years	4 years	5 years	
I	200	32.0	99.5	98.4	97.3	97.3	97.3	Reference
II	7	33.1	85.7	85.7	85.7	85.7	85.7	
III	30	33.4	86.4	82.8	82.8	82.8	82.8	26.9 (2.9–252.2)
IV	17	30.9	81.8	69.2	69.2	61.9	61.9	90.2 (6.4–1271)

[a] Hazards ratio and 95% Confidence Intervals obtained from a Cox model adjusted for age, stage and country

Fig. 4. GTN: patients treated in 1999–2001. Survival by FIGO stage, $n = 254$.

Table 15
GTN: patients treated in 1999–2001. Relapses by FIGO stage

Site relapse	All	Stage I	Stage II	Stage III	Stage IV
Local (regional)	11	7	1	2	–
Metastatic	8	3	–	1	4
Local and metastatic	–	–	–	–	–
Missing site	1	1	–	–	–
Total	20	11	1	3	4



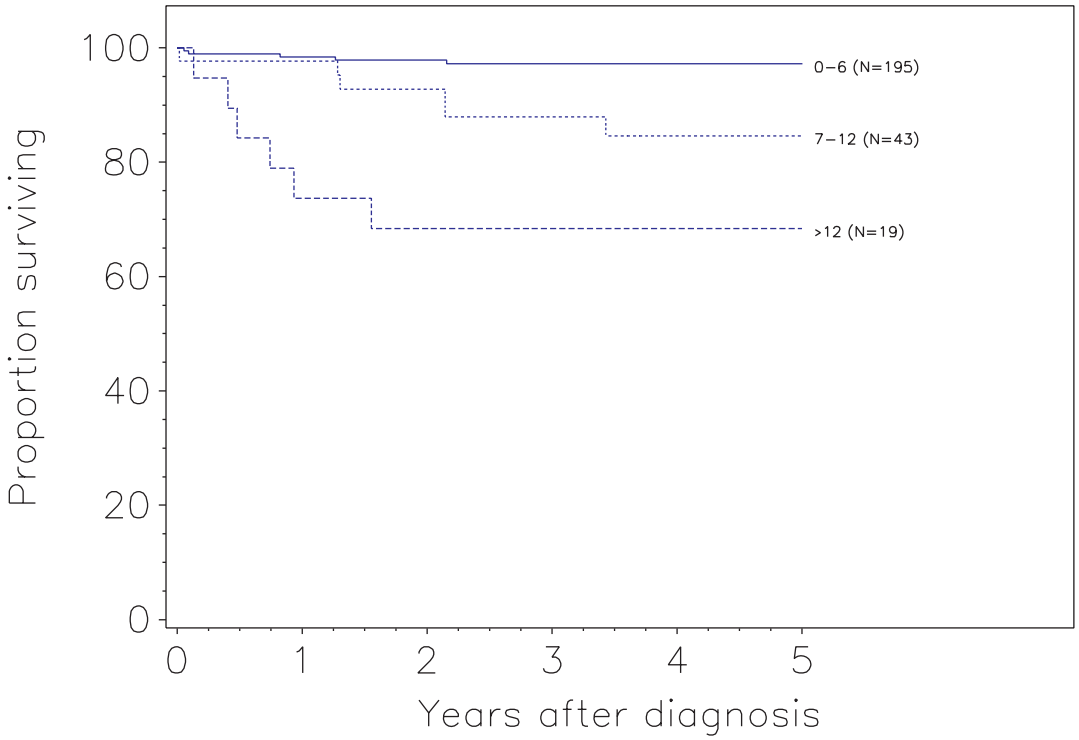
Risk score	Patients (*n*)	Mean age (yr)	Overall survival (%) at					Hazards ratio[a] (95% CI)
			1 year	2 years	3 years	4 years	5 years	
Low (0–6)	195	31.8	98.4	97.9	97.3	97.3	97.3	Reference
High (>6)	62	33.1	90.2	85.2	81.6	79.5	79.5	8.8 (2.2–35.1)

[a] Hazards ratio and 95% Confidence Intervals obtained from a Cox model adjusted for age, stage and country

Fig. 5. GTN: patients treated in 1999–2001. Survival by risk score, two groups (low/high), $n = 257$.

Table 16
GTN: patients treated in 1999–2001. Risk score by FIGO stage

Risk	All	Missing	Stage I	Stage II	Stage III	Stage IV
Missing	24	8	15	–	–	1
Low (0–6)	345	53	256	7	23	6
Intermediate (7–12)	88	5	53	4	19	7
High (>12)	26	–	4	1	9	12



Risk score	Patients (*n*)	Mean age (yr)	Overall survival (%) at					Hazards ratio[a] (95% CI)
			1 year	2 years	3 years	4 years	5 years	
Low (0–6)	195	31.8	98.4	97.9	97.3	97.3	97.3	Reference
Intermediate (7–12)	43	34.4	97.6	92.7	87.6	84.3	84.3	5.6 (1.2–25.9)
High (>12)	19	30.1	73.7	68.4	68.4	68.4	68.4	31.5 (5.4–182.2)

[a]Hazards ratio and 95% Confidence Intervals obtained from a Cox model adjusted for age, stage and country

Fig. 6. GTN: patients treated in 1999–2001. Survival by risk score, three groups (low/intermediate/high), $n = 257$.