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● *Clinical Original Contribution*

PROGNOSIS OF HUMAN CHORIONIC GONADOTROPIN-PRODUCING SEMINOMA TREATED BY POSTOPERATIVE RADIOTHERAPY

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Purpose: To clarify the controversy about the management and prognosis of human chorionic gonadotropin-producing seminoma, the records of 132 patients with abnormal human chorionic gonatropin values treated with radiotherapy were analyzed.

Methods and Materials: The records of 1169 patients with pure seminoma treated in 10 institutions were screened for serum or urinary human chorionic gonadotropin. One hundred and thirty two patients with elevated human chorionic gonadotropin were found: 96 Stage I, 20 II_A, 7 II_B, 8 III and 1 IV. Median age was 34 y., mean follow-up was 5.0 years [range 1–12 y]. All received infradiaphragmatic radiotherapy (median dose 30 Gy), 25 (2 Stage I, 11 II_A, 5 II_B and 7 III) supradiaphragmatic radiotherapy (median dose: 28.5 Gy) and 10 had also initial chemotherapy (3 Stage II_B 6 III and 1 IV). Patients were allocated to three groups according to human chorionic gonadotropin values: (a) moderate elevation: up to 10 times (104 pts), (b) high elevation: 10 to 100 times (20 pts), (c) very high elevation: over 100 times the upper limit of normal value (8 pts).

Results: The proportion of Stage I, II and III was 76%, 19%, 5% in the ME group versus 50%, 35%, 15% in the high elevation group ($p < 0.05$). In the very high elevation group there were 7 Stage I and 1 Stage IV. Of 132 patients, six died (three dead of disease, two suicides, one acquired immunodeficiency syndrome). The 5 years overall survival probability was 94%. There were seven recurrences (initial stage: 1 Stage I, 2 II_B, 3 III and 1 IV). Of these, there were one infield recurrence, 3 out of field and 3 in both sites. In 5 of 7, the human chorionic gonadotropin level was again elevated at recurrence. The 5 years recurrence-free-survival probability was 94% (98% for Stage I, 100% for Stage II_A and 65% for Stage II_B and III [$p < 0.001$ between I and II_B + III, $p < 0.05$ between II_A and II_B + III]). Four of the 7 recurrences were salvaged by chimiotherapy ± radiotherapy. In the high elevation and very high elevation groups, the 5 years recurrence-free-survival was 88%, vs. 96% for the moderate elevation group ($p = 0.10$).

Conclusion: Based on this series of patients, human chorionic gonadotropin production is not an unfavorable prognostic factor in pure seminoma. Even in the subgroups with high or very high human chorionic gonadotropin levels (who had a higher proportion of advanced stages), the prognosis remained excellent. In Stage I and II_A seminoma with abnormal human chorionic gonadotropin levels, recurrence rate after post-operative radiotherapy alone is extremely low.

Seminoma, Chorionic gonadotropin, Radiation therapy.

INTRODUCTION

Pure testicular seminoma is one of the most curable cancers, for which post-operative radiotherapy has been the mainstay of treatment for decades. In large series, this treatment has produced cure rates between 85% and 95% (4, 9, 15, 16, 27, 29, 31). In spite of these excellent results, there remain areas of controversy, among which are the prognosis and the management of Human Chorionic Gonadotropin (HCG) secreting seminoma. This subgroup

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has been estimated to comprise between 8% and 13% (2, 11, 19, 21, 24) or more (25, 26) of pure seminomas. A number of reports suggest that the overall good prognosis of seminoma is decreased in HCG-producing tumors (3, 8, 18, 22, 24, 28, 30) whereas an equal number of studies have not shown this adverse effect (1, 4, 13, 19–21, 26). In all these papers, the number of patients was relatively small, making a proper statistical evaluation difficult. To clarify this controversy we decided to analyze HCG-producing seminoma on a larger scale, in a cooperative retrospective study, grouping the experience of 10 centers in Switzerland and France. We report here 132 patients with HCG-producing seminoma treated with post-operative radiotherapy.

METHODS AND MATERIALS

Patients characteristics

The records of 1169 patients with pure seminoma treated by post-operative radiotherapy (RT) in 7 Swiss and 3 French institutions were screened for abnormal initial HCG production (HCG+). One hundred forty-four records of patients with HCG+ seminoma were identified, of which 12 were excluded from analysis for the following reasons: no pre-RT values, no RT given, mixed tumor histology, and follow-up less than 1 year. Thus, 132 patients were kept for the analysis with a mean follow-up of 5 years. They were all treated between 1976 and 1991. Data were collected on identical protocol forms in each of the 10 institutions and were reviewed and analyzed by two investigators (ROM, PAC). Patients were staged according to a modification of Maier *et al.*'s staging system (4, 17) (Table 1). Following surgical resection, diagnostic work-up included chest X ray (132 pts) and abdominal and pelvic computerized tomography (CT) (70 patients), bipedal lymphangiography (LAG) (11 patients), and 48 had both, for a total of 129 patients. In the three remaining patients, infradiaphragmatic extent of disease was assessed by intravenous pyelogram (IVP) or ultrasonography. All patients had pathology confirmation of pure seminoma. Patients' ages ranged from 17 to 67 years, with a mean of 36 years and a median of 34 years. There were 96 patients with Stage I, 20 IIA, 7 IIB, 8 III and 1 IV. All 132 patients had elevated serum HCG values; in 123 numerical values were available and in nine patients there were only qualitative indications of HCG elevation. Because of the variations of the methods of HCG determination, of the units and of the normal values during time (1976 to 1991) between and within the 10 institutions, we arbitrarily defined three categories of HCG elevation. A moderate elevation (ME) was defined as an HCG above the upper limit of normal value and up to 10 times this upper limit, using for each individual patient the method and normal value in use in his institution at the time when he was treated. A high elevation (HE) was defined as an HCG value between 10 and 100 times and a very high elevation (VHE) when it was over 100 times the upper limit of normal value. There were 104 patients in the ME (median value 4.2, range 1.1–8.8), 20 in the HE (median value 19.1, range 11.4–80.6) and eight in the VHE (median value 393.5, range 128–8600) category. The nine patients with only a qualitative HCG value were arbitrarily allocated in the ME category for further analysis.

Table 1. Staging of pure testicular seminoma*

Stage I	Tumor confined to the testes
Stage II	Evidence of tumor beyond testes and spermatic cord but limited to the infradiaphragmatic lymphatics
	A. Minimal retroperitoneal disease
	B. Bulky tumor metastases
Stage III	Tumor involving lymphatics beyond the diaphragm
Stage IV	Any tumor with extra-nodal metastases

* Modified from Maier *et al.* (4, 17).

Treatment

Radical inguinal orchiectomy was the surgical treatment in 128 patients and four had atypical surgery with trans-scrotal incision. None of the latter recurred.

All patients were treated with curative intent and received post-operative radiotherapy of infradiaphragmatic paraaortic and ipsilateral or bilateral pelvic lymph nodes. Bilateral pelvic lymph node irradiation was given in 15 patients: 4 because of prior inguinal surgery and 11 because of metastatic infradiaphragmatic lymph nodes (stage $\geq$ IIA). The median infradiaphragmatic dose was 30.0 Gy (range 18.0 to 44.5 Gy).

Twenty-five patients received supradiaphragmatic mediastinal and left supraclavicular irradiation: 2/96 Stage I, 11/20 Stage IIA, 5/7 Stage IIB and 7/8 Stage III. The median supradiaphragmatic dose was 28.5 Gy (range 20.0 to 44.0 Gy).

All patients were treated with megavoltage units with daily fractionations of 1.5 to 2 Gy, 5 days a week. None of the 116 patients with early disease (Stage I and IIA) received chemotherapy. Ten patients with advanced Stages (3/7 IIB, 6/8 III and 1/1 IV) were given chemotherapy as the initial part of their treatment, generally prior to nodal irradiation. Regimes included combinations of Cis-platinum and Bleomycin with either Etoposide or Vinblastine.

Statistics

Actuarial survival and actuarial relapse-free survival were calculated using the Kaplan-Meier method (12). The two-tailed log rank test was used to determine whether differences between actuarial curves were statistically significant at a $p \leq 0.05$ level.

RESULTS

Correlation between Stage and HCG elevation

A majority of patients (104/132, 79%) had a moderate HCG elevation (ME), as shown in Table 2a. There was a

Table 2. HCG elevation vs. Stage*

	Stage					
	I	IIA	IIB	III	IV	Total
(a) Number of patients per HCG elevation category vs. stage						
ME†	79	16	4	5	0	104
HE†	10	4	3	3	0	20
VHE†	7	0	0	0	1	8
(b) Proportion of patients per HCG elevation category vs. stage (%)						
ME†	76*	15	4	5	—	100
HE†	50*	20	15	15	—	100
VHE†	88	—	—	—	12	100

* $p < 0.05$ by Chi-Square test.
† The three HCG categories ME, HE, and VHE are defined in "Methods and Materials."

modest correlation between stage and HCG category: the proportion of Stage I, II and III was 76%, 19%, and 5% in the ME category versus 50%, 35%, and 15%, respectively, in the HE category ($p < 0.05$) (Table 2b). In the VHE group, there were 7 Stage I and 1 Stage IV.

Survival

Of 132 patients, six have died: three from seminoma (2 Stage III and 1 IV), two committed suicide, and one died from AIDS. Thus the 5-year actuarial survival rate was 94% (Fig. 1).

Recurrences

There were seven recurrences. The proportion of relapse with regard to the initial stage of these patients was: 1/96 Stage I, 0/20 Stage IIA, 2/7 Stage IIB, 3/8 Stage III and 1/1 Stage IV. Thus, the 5-year actuarial relapse-free survival rate (RFS) for all patients was 94% (Fig. 2). By Stage, the 5-year RFS was 98% for Stage I, 100% for Stage IIA, and 65% for Stage IIB and III ($p \leq 0.001$ between Stages I and IIB + III and $p \leq 0.05$ between Stages IIA and IIB + III) (Fig. 3). Details on the seven relapsing patients are given in Table 3. All patients except one had advanced initial stages. Four had high or very high initial HCG values. In 6 of 7, HCG was available at recurrence and in 5 of 6, it was found to be again elevated. There was one infield recurrence, three out of field and three in both sites. All seven patients relapsed within a 24 month period. Salvage was attempted in 6 of 7 with chemotherapy, radiotherapy, or a combination of both. Four of these patients have no evidence of recurrence at 2, 7, 8, and 10 years after retreatment.

Recurrence and initial HCG level

Actuarial relapse-free survival (RFS) was computed in the 104 patients with ME and in the 28 patients with HE and VHE. The 5-year RFS was 96% in the ME versus 88% in the HE + VHE group; the difference was not statistically significant ($p = 0.10$).

Patients with VHE HCG

Eight patients had HCG values above 100 times the upper limit (Table 4). Except for one patient who presented initially with Stage IV and who died 8 months after the initiation of an aggressive combination of chemotherapy and radiotherapy, the other patients in this uncommon HCG+ category had Stage I disease and did well, since none of them relapsed.

DISCUSSION

All major series of pure seminoma published over the past 10 years have consistently shown an excellent overall survival, in excess of 85% and up to 95% (4, 9, 15, 16, 27, 29, 31). However several controversial issues are still debated, including surveillance in Stage I (5), the manage-

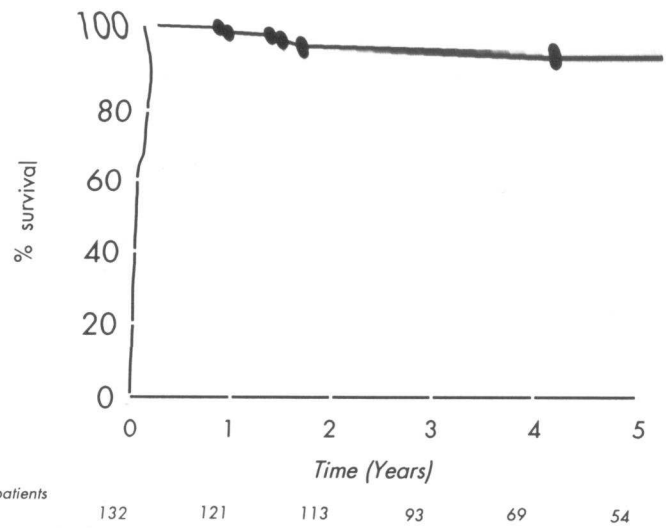

Fig. 1. Survival probability of all patients (N = 132).

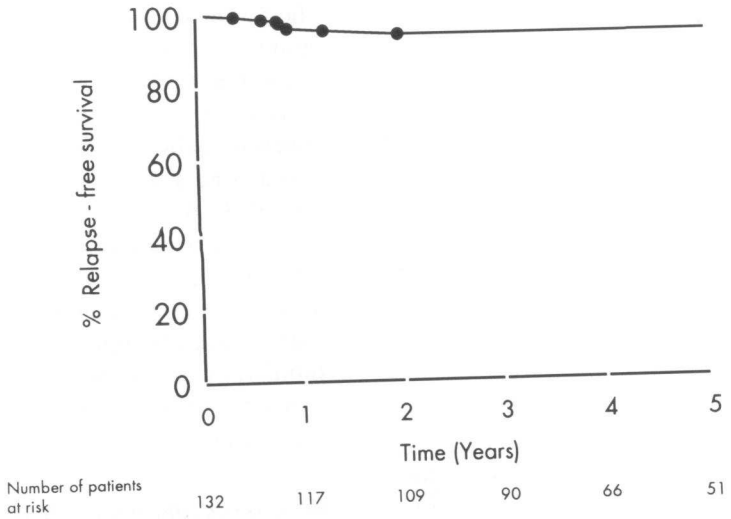

Fig. 2. Relapse-free survival probability of all patients (N = 132).

ment of bulky disease (1, 14) and the presence of HCG secreting tumors (1, 3, 4, 13, 18–22, 24, 26, 28, 30).

It has been recognized for many years that gonadotropins can be secreted by most types of testicular tumors, including pure seminoma (8, 10, 11, 23). Histological studies have shown by immunoperoxidase localisation that HCG was secreted by isolated syncytiotrophoblastic giant cells (7, 23). It is not certain that all these giant cells are trophoblastic in origin, as various morphological forms of multinucleated cells can be found in pure seminoma, including the tumor giant or "mulberry cell" and the Langhans's giant cells (3).

The frequency of HCG production in pure seminoma was reported to be between 8% and 13% (2, 11, 19, 21, 24) and even more, up to 39% to 68% (25, 26). These differences are likely to be due to the various frequency at which hormonal determinations are made in each institution, to the method of HCG determination (19, 25), to the post-surgical timing of HCG examination and possibly to the differences in stages. In our present series, 1169 charts were screened and 132 cases of HCG-secreting pure seminoma, or 11%, were found. This figure is certainly an underestimate, since in a significant proportion of the 1169 patients no initial HCG measurement had been made.

The main question regarding HCG secreting seminoma is whether or not these tumors have, stage for stage, a prognosis inferior to that of HCG-negative seminoma. Several papers have claimed a worse prognosis: in the reports from Edinburgh (8), Rotterdam (28), San Antonio (30) and the Walter Reed Hospital (18), the crude survival was between 0% and 66%. In these studies, the methods

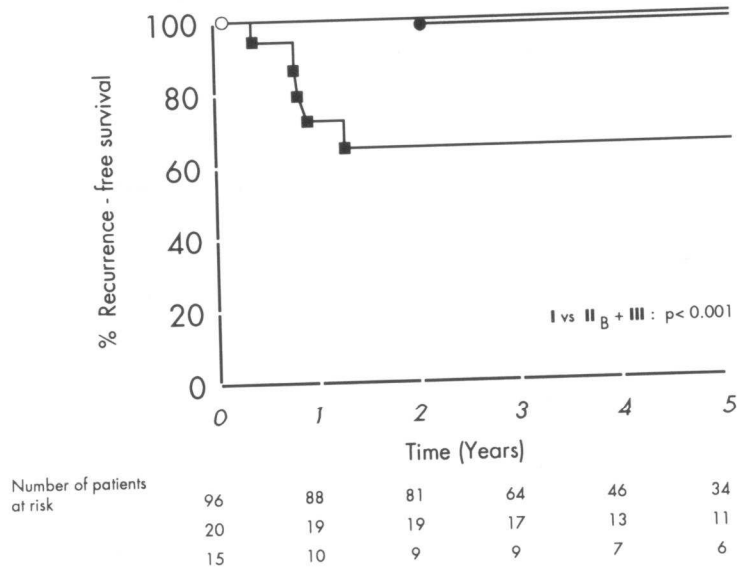

Fig. 3. Relapse-free survival probability according to Stage (Maier *et al.* [17]). Stage I$^{\bullet}$ (N = 96); Stage IIA$^{\circ}$ (N = 20); Stage IIB + III$^{\blacksquare}$ (N = 15); Stage I vs. IIB + III: $p < 0.001$.

Table 3. Patterns of failure, time to failure and salvage therapy

	Pt.	Age	In. stage	In HCG	In level*	In radiotherapy ports: Infra-diaphrag.	In radiotherapy ports: Supra-diaphrag.	HCG at failure	Site of failure	Time interval to failure (mo.)	Salvage therapy	Current status
1	BJ	49	III	HE	14×	A	−	+	IF + OOF[a]	10	CT + RT	D.O.D.
2	PL	37	IV	VHE	8600×	B	−	+	IF + OOF[b]	1[†]	—	D.O.D.
3	SR	44	III●	ME	4×	B	+	+	IF + OFF[c]	10	CT + RT	D.O.D.
4	PM	39	I●	HE	15×	A	−	+	OOF[d]	24	CT	NED, 10 y
5	HK	33	III	ME	3×	B	−	+	OOF[e]	12	CT + RT	NED 8 y
6	DC	30	IIB	ME	1.5×	B	+	−	IF	4	CT	NED, 7 y
7	HZ	53	IIB	HE	80×	A	+	NA	OOF[f]	15	RT	NED, 2 y

* Number of times the upper limit of normal value.
[†] No response.
● No initial chemotherapy (CT).
OOF = Out of field; IF = Infield.
A = Paraaortic and ipsilateral pelvic nodes; B = Paraaortic and bilateral pelvic nodes.
[a] Abdomen.
[b] Lung.
[c] Adrenal, spine, skin.
[d] Supraclavicular node.
[e] Lung.
[f] Cervical node.

of investigation (with no CT and only few LAG) were insufficient to assess the disease extent by today's standards; therefore, it is not possible to rule out an adverse prognostic effect due to advanced stage. In the more recent series of Institut Gustave Roussy (22), Aarhus (24) and St Paul's Hospital in London (3), survival was between 64% and 72%, which is less than expected in modern seminoma series. However, in the French (22) and the Danish (24) studies, the proportion of nodal metastatic disease was, respectively, 64% and 38%, which is much higher than in large seminoma papers, whereas in the British report (3), there is no information regarding the nodal status. Thus, it is not possible from any of these studies to demonstrate an independent negative prognostic effect of HCG secretion.

Conversely, an equal number of reports have failed to show an adverse effect of HCG positivity on prognosis. Data from the Harvard Joint Center (JCRT) (20), from a collaborative multicentric U.S. group (13), the Massachusetts General Hospital (MGH) (4, 21), the Royal Marsden Hospital (1), the M.D. Anderson Hospital (MDAH) (26) and Munich (19) show that in early stages, survival after postoperative RT is excellent: none of the patients with Stage I have died. In the Royal Marsden Series, eight patients with Stage II HCG+ were treated exclusively with radiotherapy: none of them failed (1).

Table 4. Patients with very high elevation of HCG (VHE)

	Pt.	Age	Stage	In. level*	RT	CT	Current status
1	PL	37	IV	8600×	41 Gy	+	D.O.D.
2	ES	41	I	1400×	30 Gy	−	NED 4 y +
3	RM	39	I	128×	30 Gy	−	NED 4 y +
4	RG	34	I	266×	26 Gy	−	NED 3 y +
5	RM	22	I	450×	25 Gy	−	NED 4 y +
6	RD	26	I	337×	30 Gy	−	NED 8 y +
7	FM	32	I	221×	27 Gy	−	NED 1 y +
8	JR	37	I	964×	30 Gy	−	NED 2 y +

* Number of times the upper limit of normal value.

Besides a possible difference in stage distribution, how can one account for the differences in prognosis between the former and latter studies? In some reports, especially the earlier ones, a proportion of patients may have presented with mixed tumors rather than pure seminoma. It should also be remembered that approximately a third of patients dying of seminoma have nonseminomatous metastases at autopsy (10). One of the major limitations of any of these 14 series is the small number of patients, with an average of 13 per study. The largest report with HCG+ pure seminoma includes only 30 patients (3).

In contrast, our present series includes 132 HCG+ patients, a number comparable to some of the recently published one-institution experience on all seminoma (9, 15, 16). Therefore, a more appropriate statistical analysis can be done to determine the significance of HCG secretion, and comparisons can be made with recent large series of unselected seminoma patients.

Our patient population with a mean age of 36 years and median age of 34 is the same as in the MDAH (31), the Princess Margaret Hospital (PMH) (27), and the JCRT (15) series. The stage distribution with 73% Stage I, 15% Stage IIA, 5% Stage IIB, 6% Stage III and 1% Stage IV is very similar to that of MGH (4), PMH (27), JCRT (15), Alberta (29) and Yale (9).

In early Stages (I and IIA), none of our patients received any chemotherapy, but all received infradiaphragmatic radiotherapy with doses comparable to those recommended in the literature (4, 15, 27, 29). Eleven of 20 Stage IIA received also elective mediastinal irradiation, a policy that was progressively abandoned in most of our

10 institutions. In more advanced Stages (IIB–III), the dose was generally higher than for early stages, and the areas of bulky disease were given additional boost, depending on individual situations. Ten of the 16 patients with advanced Stages (IIB to IV) received Platinum-based chemotherapy in addition to radiotherapy.

With the above patient and treatment characteristics in mind, the 5-year survival and relapse-free survival of 94% in our HCG+ series are as good as those of any major seminoma series (4, 9, 15, 16, 27, 29). In early stages, the recurrence rate was extremely low since only one of 116 patients with Stage I or IIA relapsed. It is striking that among these 116 patients, 21 had an HCG level classified as high in 14 (HE = from 10 to 100 times the upper limit of normal value) and very high in seven (over 100 times). Only one of these 21 patients (see patient 4, Table 3) relapsed.

In advanced stages (IIB–IV) the analysis is more difficult, since in this limited and heterogenous group of 16 patients various treatments, with or without chemotherapy, were administered. The 5-year relapse-free survival for the Stage IIB and III was 65%, a rate fairly comparable to those cited in the larger series of metastatic seminoma from the Royal Marsden Hospital (1) and Vancouver (14). The only patient with Stage IV was given an aggressive combination of chemotherapy followed by radiotherapy, but he died 8 months after the initial treatment.

It was stated in one report that the frequency of abnormal HCG level correlates with stage and tumor extent (13); whereas this was not confirmed in another paper (26). In our series, there was a moderate correlation between stage and HCG level, since the proportion of stage I was 76% in the ME category versus 50% in the HE category ($p = 0.05$). Thus, there was a slightly higher proportion of Stage II and III in the HE group. This should be weighed against the fact that 7 out of 8 patients with VHE were in Stage I. It has been sometimes suggested that a high level of HCG might be related to a worse prognosis in seminoma. However, in our experience, the 5-year recurrence-free survival in ME versus HE and VHE was 96% and 86%, an insignificant difference. In addition, there were slightly more advanced stages in the HE group.

In conclusion, from our data HCG production is not an unfavorable prognostic factor in pure seminoma. The recurrence rate after Stage I and IIA patients treated with post-operative radiotherapy and without chemotherapy was very low. Considering the respective risks of Platinum-based chemotherapy and moderate dose radiotherapy (6) and the excellent survival after irradiation, we recommend that HCG+ Stage I and IIA be treated with post-operative radiotherapy only.

For more advanced stages (Stage IIB and III), the relapse-free survival was 65%, but 3 out of 5 relapsing patients in this group were subsequently salvaged. Finally 13 of 15 Stage IIB and III are currently alive without evidence of disease. With or without HCG secretion, it is now accepted by several authors that advanced seminoma should be treated initially by a combination of chemotherapy and radiotherapy (1, 14).

Therefore, in any stage, provided that the diagnosis of pure seminoma is established by careful histological review to exclude mixed tumors, we recommend that HCG-producing seminoma should not be managed differently than HCG negative seminoma.

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