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Point of View

Combined Seminoma/Non-seminoma Should be Considered as Intermediate Grade Germ Cell Cancer (GCC)

R.T.D. Oliver, M. Leahy and J. Ong

VOGELSTEIN'S OBSERVATIONS on the cytogenetic progression of colon cancer [1] taken with Dalbagni and associates' [2] subsequent similar observations in bladder cancer, have increased understanding about how cancers develop by a Darwinian-like survival of the most successful clone generated by a cumulation of mutations/deletions of cell regulatory genes. Before the advent of molecular genetics, histopathologists anticipated this concept with the introduction of tumour grading as a measure of how far the malignancy had evolved from its tissue of origin.

Despite many attempts [3–5], germ cell cancers (GCC) have been one group which have never been satisfactorily graded. Today, few dispute that carcinoma *in situ* (CIS), or "gonocytoma *in situ*", as it has recently been named [6], because of the principal cell's morphological similarity with primordial germ cells [7], is the precursor of all GCC's with the possible exception of spermatocytic seminoma [8] and the majority of prepubertal teratoma differentiated and embryoblastoma [9]. That the heterogenous subtypes of non-seminoma (malignant teratoma) develop by evolution from CIS is supported by data showing that the median DNA content of CIS cells is 4.2N [10], that of seminoma is 3.6N and of non-seminoma is 2.7N [11, 12]. Recent studies have suggested that the precursor cell is the tetraploid meiotic mid prophase spermatocyte [13]. Interphase cytogenetics have demonstrated that there is reduction in copy numbers of chormosomes 12 and 15 during the evolution from seminoma (S) to non-seminoma (NS) [14], although in some cases, this occurred at the CIS stage [15]. Additional losses have been observed in transition from embryonal carcinoma to teratoma [16].

Clinical evidence that transformation can occur after a significant amount of seminoma has developed comes from the study of combined tumour patients whose median age is halfway between that of seminoma and non-seminoma [4]. Further support comes from study of unselected patients treated by the Anglian Germ Cell Tumour Group, the outcome of which has been been reported elsewhere [17–20]. Patients were divided into three subgroups on the basis of histology reviews i.e. pure seminoma—S (40%, median age 37 years), combined seminoma/non-seminoma—S + NS (15%, median age 32 years) and pure non-seminoma—NS (45%, median age 29 years).

For three clinical parameters, that is the proportion of stage 1 patients, their relapse rate on surveillance, and cure rate of poor risk high marker subgroup metastatic disease patients, there is an intermediate behaviour of the combined tumour (Table 1).

In addition, combined tumours are intermediate between seminoma and non-seminoma in terms of the proportion of patients with stage 1 disease for a given period of delay in diagnosis (Table 2). The higher frequency of seminoma in the patients with shorter delay would also support the concept of non-seminoma arising as a later stage in the process, although the high proportion of seminomas in those with prolonged delay demonstrates that there is a substantial proportion of patients with a block to progression. This is also supported by the observation that metastatic S and S+NS patients have age of

Table 1. Combined tumours as an intermediate prognosis subgroup of testicular germ cell tumours

	Seminoma $n = 248$	Combined seminoma/non-seminoma $n = 116$	Non-seminoma $n = 241$
Median age stage 1	36 years	31 years	29 years
Median age metastatic patients	42 years	37 years	29 years
Proportion presenting in stage 1	79%	51%	41%
Relapse stage 1 adjuvant	1%	6%	0%
Relapse stage 1 surveillance	23%	31%	38%
Primary cure of all metastatic patients	91%	93%	86%
Proportion of metastatic cases with high markers	0%	16%	21%
Cure rate low markers	91%	94%	92%
Cure rate high markers	-	89%	65%

Correspondence to R.T.D. Oliver.
The authors are at the Department of Medical Oncology, The Royal London Hospital Medical College, London E1 1BB, U.K.
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Table 2. Influence of delay on germ cell cancer histological subtype and proportion with stage I disease

	Months			
	≤1	2–3	4–11	>11
Seminoma				
Proportion stage I	79% (*n*=47)	58% (*n*=48)	67% (*n*=54)	50% (*n*=40)
Proportion in delay cohort	49%	34%	34%	53%
Combined seminoma and non-seminoma				
Proportion stage I	75% (*n*=20)	56% (*n*=34)	27% (*n*=41)	36% (*n*=11)
Proportion in delay cohort	21%	24%	26%	15%
Non-seminoma				
Proportion stage I	76% (*n*=29)	33% (*n*=100)	21% (*n*=63)	13% (*n*=24)
Proportion in delay cohort	30%	42%	40%	32%

diagnosis 6 years later than stage 1 patients, while metastatic NS patients have diagnosis at same age as stage 1 NS (Table 1).

The long exposure to smoking in S and S+NS may explain why smoking is only prognostically significant in those patients (Table 3). A similar effect has been observed in melanoma, breast, bladder and head and neck cancer (for refs see [21]). It raises an important practical issue as, in the only study reported, cured GCC patients continued smoking more than the normal population [22].

The initial British Testicular Tumour panel classification did attempt to make a comment about grading, although neither the second version of this [4] nor the currently accepted UICC/WHO classification [5] address this issue. The clinical observations reported in this paper suggest that combined S and NS could be considered as intermediate or G2 germ cell cancer while NS could be considered as an undifferentiated or G3 germ cell cancer in that it contains no cells recognisably similar to those of the primary gonocytoma cell of origin. These most closely resemble the cells in seminomas which can thus be considered the equivalent of G1 germ cell cancer.

This classification does not take into consideration the WHO subgroupings based on the type of fetal tissue expressed. However, given their large number and limited value in prognostication, it is more logical to consider them as an extra dimension to GCC classification like vascular or lymphatic invasion. Bladder cancer provides a possible way to designate this separate dimension. The term metaplasia is used to describe bladder tumours with areas of squamous or glandular epithelium. Some have both, while others can be even more polymorphic with cartilage and even at the extreme choriotrophoblast. There were three such cases in a series of 108 metastatic bladder cancers reviewed by one of us [23] little different from the frequency of pure choriocarcinoma of the testis. Use of the term metaplasia to describe the type of fetal differentiation present in any GCC, whether G1, 2 or 3, would enable the new classification to retain all the currently accepted sub-groups, i.e. trophoblast, yolk sac, teratocarcinoma as well as make it easier to understand how some seminomas can express hCG and aFP.

Mature teratoma, most frequently seen today after chemotherapy has destroyed the gonocytoma elements [24], does not easily fit this classification. A possible explanation is that those occurring spontaneously have rejected the gonocytoma elements including CIS [21]. In the cervix, spontaneous regression of CIN has been demonstrated in 17–62% of patients [25] which is more frequent than in established invasive tumours. Evidence that this may also be the case in GCC comes from the observations of Daugaard and associates [26]. Although 42% of their patients with retroperitoneal extra gonadal GCCs had CIS in testis biopsy, an additional 35% had such severe atrophic germinal epithelium that there was no CIS and virtually no germ cells.

Table 3. Impact of cigarette smoking on disease-free survival of germ cell tumours

	Seminoma or combined seminoma/non-seminoma		Non-seminoma		
	No. of cases	Disease-free survival	No. of cases	Disease-free survival	
>10 per day	37	68%	27	70%	χ^2 0.14 *P*=ns
≤10 per day	82	94%	81	70%	χ^2 16.7 *P*<0.0005
Significance	χ^2 13.9 *P*<0.0005		χ^2 0.08 *P*=ns		

CONCLUSION

Orchidectomy remains the standard diagnostic procedure for testicular swellings. As this analysis has established that combined seminoma/non-seminoma behaves clinically as an intermediate prognosis germ cell cancer, particularly in respect of prognosis of stage 1 tumours, there is a need for confirmatory studies in larger unselected databases to investigate the interaction of this prognostic factor with others such as vascular invasion, tumour marker expression and smoking habits.

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