Pathological Characteristics of Prostate Cancer Occurring in Younger Men: A Retrospective Study of Prostatectomy Patients

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OBJECTIVE To determine if differences exist in the pathological characteristics of prostate cancer occurring in younger men as compared to the disease when it occurs in older men.

METHODS A retrospective cohort study was conducted on prostatectomy specimens from the prostate cancer database of a single large Australian pathology practice which services a large proportion of hospitals within 1 state. Data were extracted regarding the pathological characteristics of the cancers and a univariate analysis was conducted against 2 age cutoffs.

RESULTS Data were extracted for all prostatectomy specimens between 2011 and 2017 in 11,551 men. One hundred and thirty-two men were 45 years old and younger, and 545 were 50 years old and younger. Statistically significant differences were found in a number of pathological characteristics. Younger men had lower grade group disease, and within that had less adverse pathological characteristics. In particular, even after controlling for confounding in men 45 and younger, in Grade Group 2 disease there was a lower risk of extra prostatic extension (17.5% vs 34.4%, $P = .003$), and lymph node involvement (0% vs 0.8%, $P = .006$), with trends toward superiority in other domains.

CONCLUSION Our results demonstrate that prostate cancer in younger men tends to be lower grade and stage disease compared to older men. This is in contrast to persistent views within the urological community and may have an impact on disease management in younger men. UROLOGY 134: 163–167, 2019. © 2019 Elsevier Inc.

BACKGROUND

Prostate cancer is a common disease: the incidence is predicted to be over 17,700 cases per annum in 2018 in Australia,[1] and over 164,000 per annum in 2018 in the United States.[2] Although predominantly a disease of older men (with incidence increasing rapidly over age 55[3]), approximately 10% of cases are diagnosed in men under the age of 60,[4] with cases in men as young as 22 reported.[5]

Historically, the diagnosis of prostate cancer in a younger man was a poor prognostic indicator, particularly with regards to overall survival. Cancer registries and large epidemiologic studies from the Pre-Prostate Specific Antigen (PSA) era showed that young men with prostate cancer routinely had worse outcomes than older men, with higher grade, less differentiated, and more advanced tumors correlating with meaningfully worse clinical outcomes.[6-8] However, the advent of PSA testing (and PSA screening in either a systematic or nonsystematic way) has radically altered the pattern of diagnosis of prostate cancer, with marked increases in the rates of diagnosis of lower stage cancer in younger men in particular.[9] Of note, more recent interrogations of the Surveillance, Epidemiology, and End Results (SEER) registry in the post-PSA era have shown that the gap between the prognosis in younger and older men has shrunk very considerably.[4]

Not unreasonably, and most likely influenced by the previously poor prognosis of prostate cancer in younger men, a widespread belief has persisted amongst clinicians that when prostate cancer occurs in younger men it must be in some ways different to the same disease occurring in older men.[10] Anecdotally, the commonly held belief is that the disease found in a younger man must be more aggressive than the same disease found in an older man. Such a belief could easily affect clinical decision-making. If a clinician expects to be treating a more aggressive disease, they are more likely to pursue more aggressive treatment of the disease (eg, being less willing to perform a nerve sparing approach at operation, or electing to perform a nodal dissection, or irradiating a slightly larger field in order to minimize the risk of missing viable tumor).

Conflicts of Interest: *None.*

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Needless to say, such decisions have implications (eg, opting to avoid a nerve spare has negative implications in terms of potency and continence), which are particularly relevant in treating a younger man.

Although these beliefs are widespread, the evidence published to date does not support this. Several studies have been conducted, including 1 large study using epidemiologic data,[4] several small case series,[5,11,12] and at least 3 larger institutional case series.[13-15] Each of these studies, however, can be criticized from a methodological standpoint. The largest study to date did not report the grade group of disease, instead clustering the grade groups into high, medium, and low grade (an artefact of the database used),[4] and lacks the detail to be easily applicable for individual patients in normal practice. Conversely, although many of the smaller series' did report adequate detail for conclusions to be reached, their sample sizes were underpowered to detect any subtle differences. The larger institutional studies by Loeb et al, Becker et al, and Gielchinsky et al were all methodologically rigorous, however the cohorts were collected from single institutions over long periods of time (some cases dating back as far as 1975), thus incorporating several revisions in the Gleason Grading system and pooling patients from both before and after the PSA era. Similarly, each of these institutions is tertiary referral centers within their area, and therefore it is plausible that there are patient selection factors in these cohort which may not be applicable to a general cohort.

Therefore, the question for a urologist working in a nontertiary center today is: although the bulk of evidence in the PSA era suggests that prostate cancer in younger men is the same as in older men, is the evidence from tertiary institutions generalizable to routine practice, and how do I council my patient?

OBJECTIVE

This study aims to determine if differences exist in the pathological characteristics of prostate cancer when in occurs in younger men based on a representative, recent, multi-institutional cohort of patients undergoing radical prostatectomy.

METHODS

Design, Setting, and Participants

This study was conducted as a retrospective audit of prospectively collected data from the database of a large private laboratory. Douglass Hanly Moir Pathology is the largest private pathology provider in Australia, and their database has been maintained prospectively since the 1990s. However in this study, for practical reasons, data were extracted between 2011 and 2017. Over the course of this study, a total of 9 pathologists reported prostatectomy specimens at Douglas Hanly Moir with regular internal quality checks performed in order to maintain homogeneity of the reporting standards.

The only exclusion criteria were not having prostate cancer on final histopathology. Although the pathological analysis was conducted in a single institution, patient data were collected from multiple centers across Australia ranging from tertiary centers in Sydney and Melbourne, to small regional and rural hospitals. It is worth highlighting that although the private health system in Australia is a partially user-pays system, it also has high penetrance in the prostate cancer disease in Australia, with some recent studies demonstrating that a large majority of men will have treatment for their prostate cancer in the private sector.[16] As such we believe that our sample will be broadly representative of Australian men.

Outcome Measurement and Statistical Analysis

Following ethical review and approval, the data were deidentified and extracted from the database for each of the years of the study. Data fields analyzed included the age of the participant at the time of operation, characteristics of the tumor (eg, tumor type, Gleason Grade, tumor volume, location of the tumor within the prostate etc) and some ancillary data such as the pathological T stage.

Data were reformatted and where appropriate transformed in order to be analyzable. The main example of this was transforming the raw Gleason score into the International Society of Urological Pathology Grade Group ranging from 1 to 5.[17]

Two different definitions of "younger" men were used in this study: men 45 and under, and men 50 and under. The age cutsoffs chosen reflect the smallest subsets of the cohort in which statistically significant findings were made. The reason that 2 separate age cutoffs was to minimize the risk of Type II error caused by the relatively small group of men under 45. It is worth noting that in other studies, age cutoffs of 55 to define younger men are more common,[11] however there is no consensus or biological basis to determine what constitutes a "younger man" with regards to prostate cancer.

For each age cutoff we present the statistical difference compared to the remainder of the cohort (ie, the statistical difference between men 45 and under vs men over 45), and also the mean values for the whole cohort. As the groups represent small proportions of the total cohort, the effect of these groups on the overall cohort is minimal.

Data were analyzed in IBM SPSS Statistics version 20.0 (Armonk, New York, NY). Univariant analysis was conducted for both age cutoffs. For continuous data, the Student's *t* test was used, and chi-squared tests for ordinal data.

RESULTS

Valid data were collected on 11,551 men. Of these 132 were 45 years old and younger (1.1%), and 545 were 50 years old and younger (4.7%). The age distribution shows a peak of men at age 63, with a slight left skew to the data.

With regards to the physical properties of the prostate and the tumor, as would be expected, younger men had smaller prostates with smaller index lesions (Table 1).

With regards to grade of tumors, as shown in Table 2, younger men tended to have lower grade group disease than older men. The differences were statistically significant (men 45 and younger: $\chi^2 = 78.0$, $P < .001$; men 50 and younger: $\chi^2 = 135.6$, $P < .0010$).

Interestingly, although the proportion of high-grade disease (ie, Gleason pattern 4 or 5) was lower in younger men as compared to older men, these differences were not statistically significant (men 45 and younger: mean percentage High-Grade 19.6 (15.7-23.3), $t_{11155df}$ −0.609, $P = .543$; men 50 and younger: mean percentage High-Grade 26.6 (24.3-29.1), $t_{11155df}$ −0.971, $P = .332$; all men: mean percentage High-Grade 50.0 (41.92-61.9)). This apparent discrepancy is explained by the preponderance of lower grade disease in younger men, and subgroup analysis of each grade group

Table 1. Physical properties of prostates and tumors

	Men 45 and Younger		Men 50 and Younger		All Men
	Mean (95% CI)	Difference*	Mean (95% CI)	Difference†	Mean (95% CI)
Prostate weight (g)	39.05 (37.43-40.66)	$t = -8.0$, $P < .001$	41.38 (40.52-42.30)	$t = -13.9$, $P < .001$	53.04 (52.67-53.42)
Tumor volume (cm^3)	1.21 (0.87-1.77)	$t = -3.3$, $P = .001$	1.38 (1.19-1.61)	$t = -5.2$, $P = .001$	1.94 (1.90-1.99)

* Difference measured between men aged 45 and younger and the remainder of the cohort.
† Difference measured between men aged 50 and younger and the remainder of the cohort.

Table 2. Grade group distribution based on age category

	Men 45 and Younger *n* (Percentage)	Men 50 and Younger *n* (Percentage)	All Men *n* (Percentage)
Grade Group			
1	26 (19.7)	74 (13.6)	611 (5.5)
2	86 (65.2)	348 (63.9)	5903 (52.9)
3	18 (13.6)	87 (16.0)	2953 (26.5)
4	0 (0)	15 (2.8)	442(4.0)
5	2 (1.5)	21 (3.9)	1247 (11.2)

confirmed that there are not statistically significant differences between the age groups once stratified by grade group.

By comparison, there were differences in the percentage of patients with extra prostatic extension (EPE), lymph node positivity (60.3% of men had lymph node dissections), lymphovascular invasion, and seminal vesical involvement, with all 4 parameters statistically significantly seen more frequently in the older age group. As shown in Table 3, there were marked differences in these pathological characteristics.

In order to control for the possibility of confounding caused by the unequal distribution of lower grade group disease, a subgroup analysis was conducted of these same pathological characteristics in only Grade Group 2 disease (to minimize the risk of confounding, men with Grade Group 1 disease were excluded from this analysis as these adverse pathological features rarely if ever occur within these patients). Within this subgroup analysis, the striking feature is the even lower rate of EPE and intraductal carcinoma in younger men as compared to older men. Beyond this, the similarities in the other pathological characteristics probably reflect the limited sample sizes and relative rarity of positive findings. These findings are shown in Table 4.

Conversely, an analysis of the same characteristics for higher grade group disease (Grade Groups 3-5) only yielded statistically significant differences with regards to the risk of intraductal carcinoma. In this analysis, the 15 of 123 men age 50 and under within the subgroup had Intraductal Carcinoma (12.2%) as compared to 1029 of 4642 of men overall (22.2%, χ^2_{1df} 7.282, $P = .006$). Although a similar difference in the proportions was apparent in the men 45 and under (2 of 20, 10%), the difference was not statistically significant (χ^2_{1df} 1.723, $P = .28$), but this may well reflect the small sample size in the sub group and the limited event rate.

DISCUSSION

Our study correlated well with the findings by others. No matter how the data are approached, it appears that the pathological characteristics of prostate cancer when it occurs in younger men are either the same, or somewhat more favorable than when it occurs in older men. In the first instance, it is apparent that prostate cancer in younger men tends to be lower grade: in this cohort 77.5%-84.9% of younger men had

Table 3. Pathological characteristics of cancers based on age category

		Men 45 and Younger		Men 50 and Younger		All Men
		n (Percentage)	Difference*	*n* (Percentage)	Difference†	*n* (Percentage)
Extra prostatic extension	Negative	106 (80.3)	$\chi^2 = 38.9$, $P < .001$	387 (71.0)	$\chi^2 = 69.7$, $P < .001$	6003 (53.7)
	Focal	13 (9.8)		64 (11.7)		1858 (16.6)
	Established	13 (9.8)		94 (17.2)		3309 (29.6)
Lymph nodes (when biopsied)	Not involved	49 (96.1)	$\chi^2 = 32.3$, $P < .001$	254 (94.8)	$\chi^2 = 42.7$, $P < .001$	6547 (94.0)
	Involved	2 (3.9)		14 (5.2)		418 (6.0)
Seminal vesical involvement	Not involved	128 (97.0)	$\chi^2 = 6.6$, $P = .01$	524 (96.1)	$\chi^2 = 21.7$, $P < .001$	10,100 (90.4)
	Involved	4 (3.0)		21 (3.9)		1070 (9.6)
Lymphovascular invasion	Absent	129 (97.7)	$\chi^2 = 32.3$, $P < .001$	532 (97.6)	$\chi^2 = 13.1$, $P < .001$	10,503 (94.0)
	Present	3 (2.3)		13 (2.4)		667 (6.0)
Intraductal carcinoma	Absent	129 (97.7)	$\chi^2 = 11.6$, $P < .001$	522 (95.6)	$\chi^2 = 31.6$, $P < .001$	9853 (86.6)
	Present	3 (2.3)		23 (4.4)		1317 (13.4)

* Difference measured between men aged 45 and younger and the remainder of the cohort.
† Difference measured between men aged 50 and younger and the remainder of the cohort.

Table 4. Subgroup analysis of pathological characteristics of cancers in Grade Group 2 disease based on age category

		Men 45 and Younger		Men 50 and Younger		All Men
		n (Percentage)	Difference*	*n* (Percentage)	Difference†	*n* (Percentage)
Extra prostatic extension	Negative	71 (82.6)	$\chi^2 = 11.43$, $P = .003$	268 (77.0)	$\chi^2 = 21.6$, $P < .001$	3873 (65.6)
	Focal	9 (10.5)		37 (10.6)		1011 (17.1)
	Established	6 (7.0)		43 (12.4)		1019 (17.3)
Lymph nodes (when biopsied)	Not involved	32 (100.0)	$\chi^2 = 10.31$, $P = .006$	147 (98.0)	$\chi^2 = 20.0$ $P < .001$	3168 (99.1)
	Involved	0 (0.0)		3 (2.0)		28 (0.9)
Seminal vesical involvement	Not involved	86 (100.0)	$\chi^2 = 1.97$, $P = .266$	344 (98.9)	$\chi^2 = 1.9$, $P = .254$	5773 (97.8)
	Involved	0 (0.0)		4 (1.1)		130 (2.2)
Lymphovascular invasion	Absent	86 (100.0)	$\chi^2 = 0.77$, $P = 1.000$	347 (99.7)	$\chi^2 = 1.49$, $P = .370$	5851 (99.1)
	Present	0 (0.0)		1 (0.3)		52 (0.9)
Intraductal carcinoma	Absent	85 (99.1)	$\chi^2 = 2.55$, $P = .129$	340 (97.7)	$\chi^2 = 5.15$, $P = .020$	5618 (95.5)
	Present	1 (0.9)		8 (2.3)		285 (4.8)

* Difference measured between men aged 45 and younger and the remainder of the cohort.
† Difference measured between men aged 50 and younger and the remainder of the cohort.

Grade Group 1 or 2 disease, as compared to 58.4% of the whole cohort. This should be reassuring when counselling a young man: the likelihood is that any low-grade disease found on biopsy is likely to be low-grade disease rather than representing under-reporting of higher grade disease.

However, even once the preponderance of lower grade disease is controlled for, there are some favorable characteristics of the tumors found in younger men. In particular, the substantially decreased risk of EPE and intraductal carcinoma are robust findings which become more pronounced in subgroup analysis. Given that the starting hypothesis was that if one is expecting to find aggressive disease one may adopt a different management approach, we would argue that the opposite ought to be true. Namely, in the treatment of a younger man with Grade Group 2 disease, the risk of EPE may be as low as 17% as compared to over 34% in an older man.

Although outside the scope of our study to comment definitively, it seems plausible that what we observed was lead time effect. Namely that if given longer with the malignancy in situ, that a proportion of the men without adverse pathological features would have gone on to develop them. This could well explain how apparently similar disease in older men seems to be associated with more adverse pathological characteristics. However, this too would fit with the basic proposition that prostate cancer in younger men is the same disease as in older men, but is likely to be at a more clinically favorable stage of its natural history if detected in a younger man.

There are some limitations in this study, most obviously that this database collected specimens exclusively from men who have undergone a prostatectomy. Although this does improve the quality of the data and decrease the probability of missing positive histopathological findings as compared to a study including biopsy specimens, it also means that we cannot be sure that there are not different pathological characteristics in the men who do not proceed to prostatectomy as compared to those who do (ie, those who proceeded to watchful waiting, active surveillance or radiotherapy).

Similarly, although this is the largest multicenter study which has been conducted to date, the sample size in the smaller subgroups was not adequate to prove the existence of difference in the pathological characteristics which occurred relatively infrequently (eg, for men 45 and under with lower grade group disease, there were only 112 patients in total. For an event such as lymphovascular invasion, which occurred in less than 1% of men, there was a low likelihood of any men exhibiting the characteristic). However, reaching a reasonable power for these findings would require prohibitively large same sizes, and we do not believe that this is possible without massively expanding the cohort (eg, achieving 80% power for a comparison of the risk of lymphovascular invasion for men 45 and under with Grade Group 2 disease would require 315 patients in each arm, and at present there are 86 in this subgroup).

It is also worth noting that our study includes data from before and after the implementation of the revision of the Gleason Grading system following The 2014 International Society of Urological Pathology Consensus Conference on Gleason Grading of Prostatic Carcinoma.[17] The exact effect of the revision on our data are not clear, however unless we assume that this effect would be unevenly distributed between different age groups there is no reason to believe that it will impact our conclusions.

Finally, we were not able to link any of our findings to clinical outcomes for individual patients (eg, evidence of biochemical recurrence). Therefore, although we reasonably expect that the absence of negative pathological characteristics in younger men will correlate with improved outcomes, we cannot prove this from within our own study. Given that other studies have reported on prognosis,[4,13,15] it is not clear how much this would add to the present study.

However, despite these limitations, this study remains the largest multicenter study of its kind. Our findings align with the findings of other studies (both large multicenter epidemiologic studies and smaller single center studies), in addition to being relatively robust in their own right. We have also considered the histopathological details of the disease in greater depth than previous studies, which we believe will be particularly relevant to clinicians in interpreting pathology reports.

Further research in this field could be directed toward overcoming the limitations of this study, such as linking

our findings with follow-up outcomes, and confirming that the adverse pathological findings studied here correlate with disease outcomes in a younger population in a similar way to their effect in an older population. We are also interested in linking our findings from this study to biopsy data to determine how predictive biopsies were for the results at prostatectomy. However, we do not believe that our principal finding is likely to change significantly, and expect that additional efforts in this direction would likely reinforce our key findings.

CONCLUSION

Our study aimed to determine whether there are pathological differences between prostate cancer when it occurs in younger men as opposed to older men, and based on our findings we can say with confidence that in the post-PSA era any such differences favor younger men. Although our study does have limitations, with data from over 11,500 men, this is the largest multicenter study of its kind and validates work previously done in this field. This should add weight to and resolve, beyond any reasonable doubt, the generalizability of previous studies that have sought to answer this question.

Based on our study, younger men should be reassured that that their cancer is likely to be lower grade, and less likely to have adverse pathological characteristics than the same disease occurring in an older man. Similarly, clinicians should be reassured that a finding of prostate cancer in younger men does not necessarily represent more aggressive disease, and that treatment options should be offered based on the same treatment algorithms as other patients rather than treating against the expectation that the disease is worse than it appears.

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