

Prognostic impact of age at diagnosis & primary grade on high Gleason score Prostate cancer patients

CHANDANA JAVVAJI, MBBS

SABY GEORGE, MD

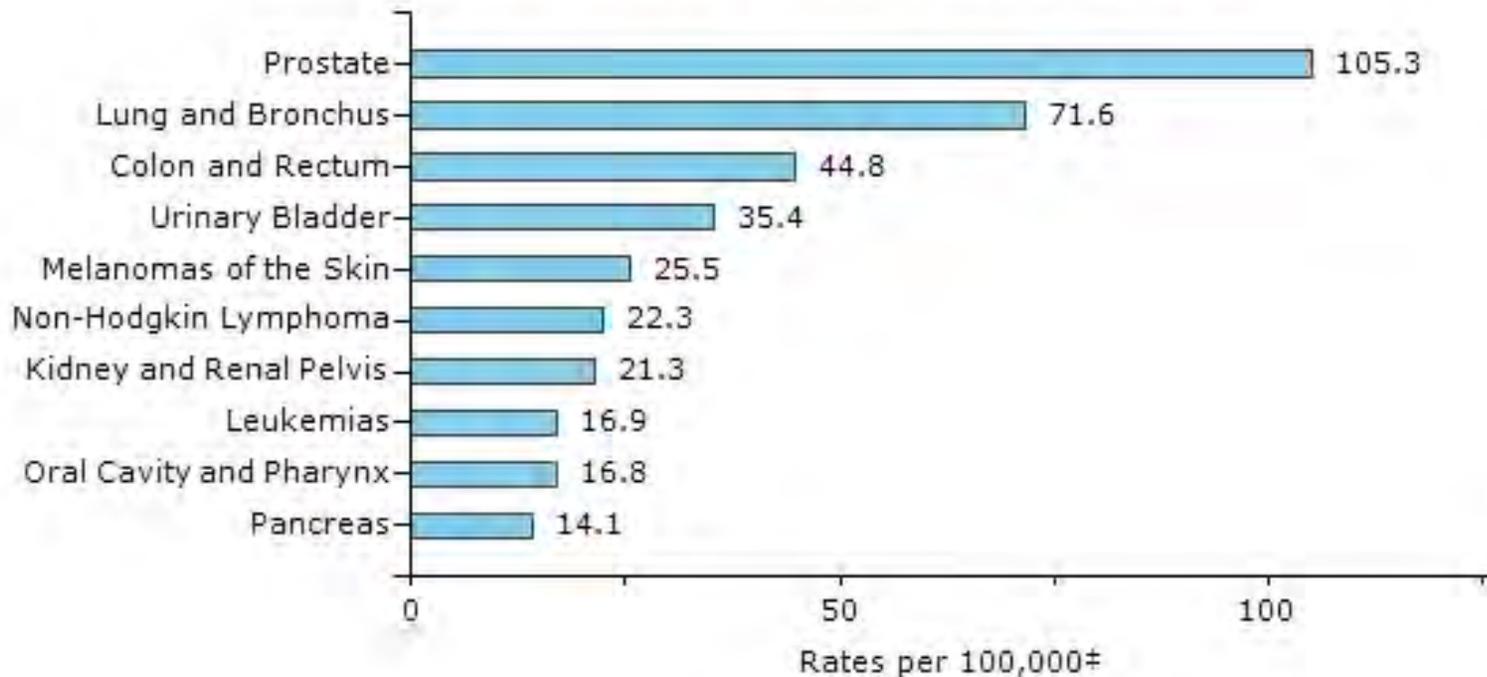


Prostate cancer

- Second most common cause of cancer in men
 - Second leading cause of cancer death among men
 - Most cases are clinically insignificant
 - Incidence increases rapidly with age
 - Adenocarcinoma comprises >95%
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Age-Adjusted Invasive Cancer Incidence Rates

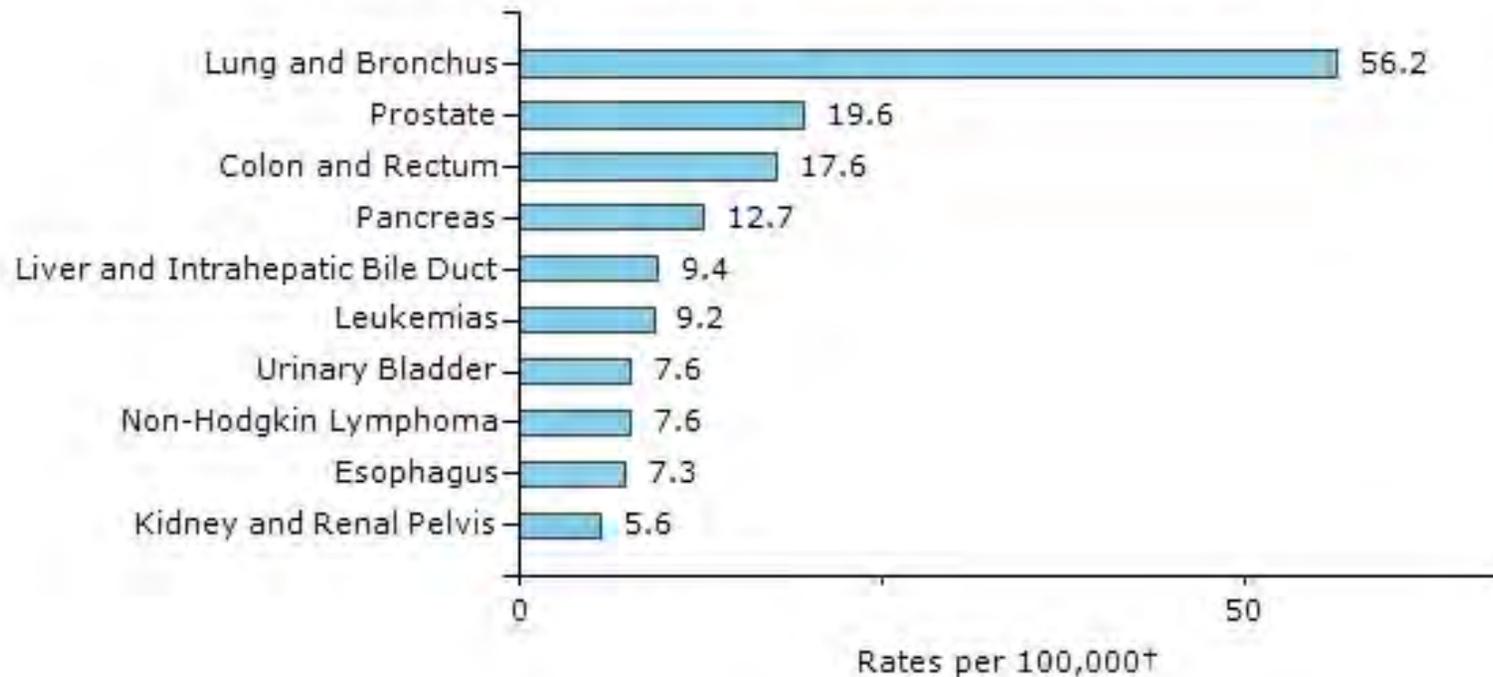
Top 10 Cancer Sites: 2012, Male, United States—All Races



United States Cancer Statistics: 1999–2012 Incidence and Mortality Web-based Report.
(www.cdc.gov/uscs)

Age-Adjusted Cancer Death Rates

Top 10 Cancer Sites: 2012, Male, United States—All Races



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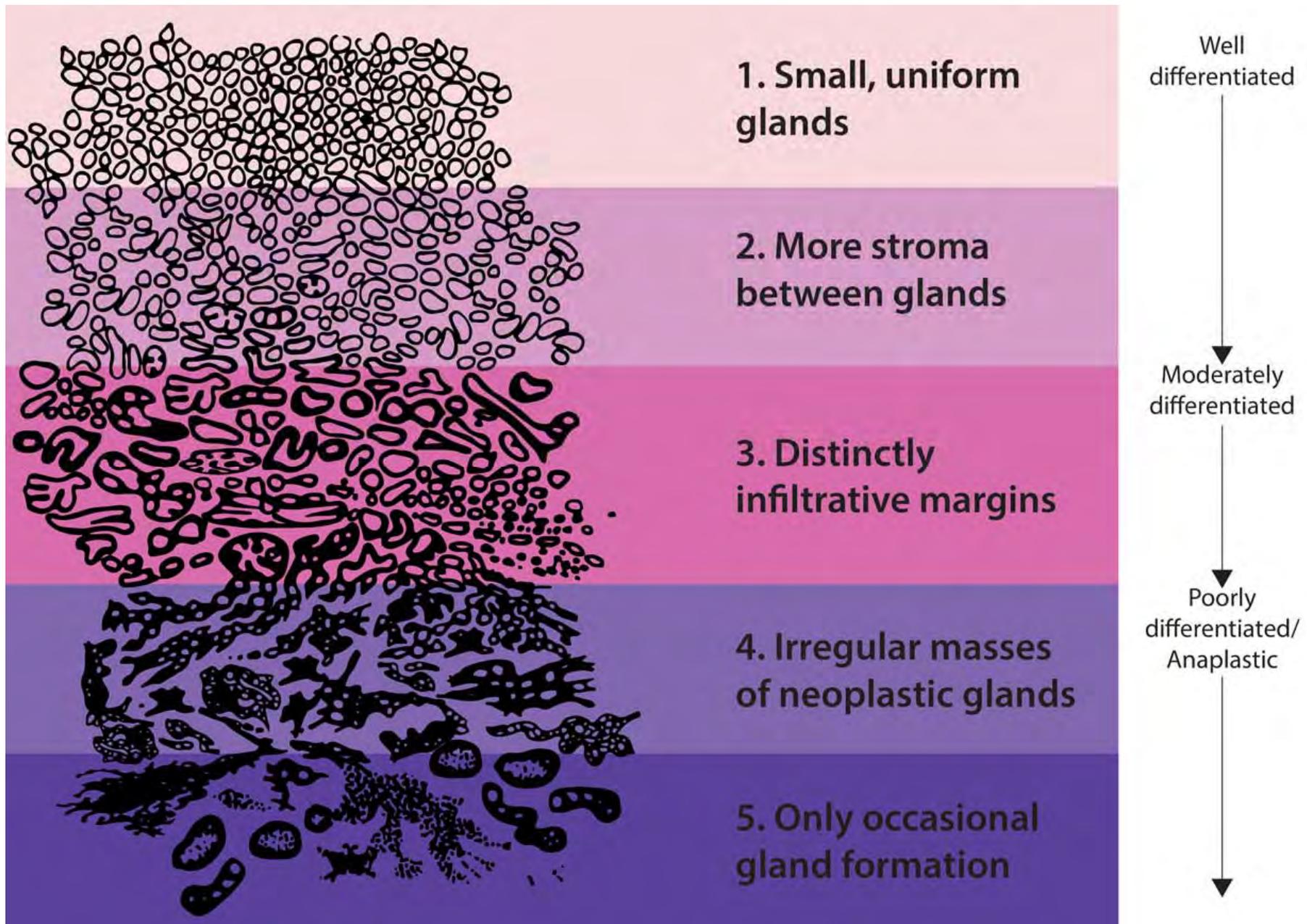
Risk factors for prostate cancer

- Age
 - BRCA2 mutation
 - Race
 - Family History
 - Dietary factors
 - Lifestyle factors
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Gleason Score

- For Prostate adenocarcinomas, the degree of differentiation has prognostic significance
 - Pathologists judge biopsy specimens using Gleason grading system
 - Five distinct grades were originally described by Dr. Gleason using a scale from 1-5.
 - Grade 1 lesions: most differentiated
 - Grade 5 lesions: least differentiated
 - Prostate cancers tend to be heterogeneous, with 2 or 3 grades occurring within a typical Prostate gland.
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Gleason grading system



How to calculate Gleason score?

- When a pathologist looks at Prostate cancer specimens under a microscope they identify the most common grades.
- The most common histologic grade is called **Primary grade**.
- The second most common histologic grade is called **Secondary grade**.



Example

S: Primary
Grade

Secondary
Grade

Gleason
Score

$$5 + 4 = 9$$

$$4 + 5 = 9$$

➤ Gleason score ranges from **2** (1+1) to **10** (5+5)



Gleason score summary

Gleason score	What does this score mean?
2–6	The cancer is likely to grow and spread very slowly. If the cancer is small, many years may pass before it becomes a problem. Thus, you may never need cancer treatment.
7	The cancer is likely to grow and spread at a modest pace. If the cancer is small, several years may pass before it becomes a problem. To prevent problems, treatment is needed.
8–10	The cancer is likely to grow and spread fast. If the cancer is small, a few years may pass before the cancer becomes a problem. To prevent problems, treatment is needed now.

Treatment options for Prostate cancer with localized disease

- Radical Prostatectomy
- Radiation therapy (External beam radiotherapy/Brachytherapy)
- Active Surveillance

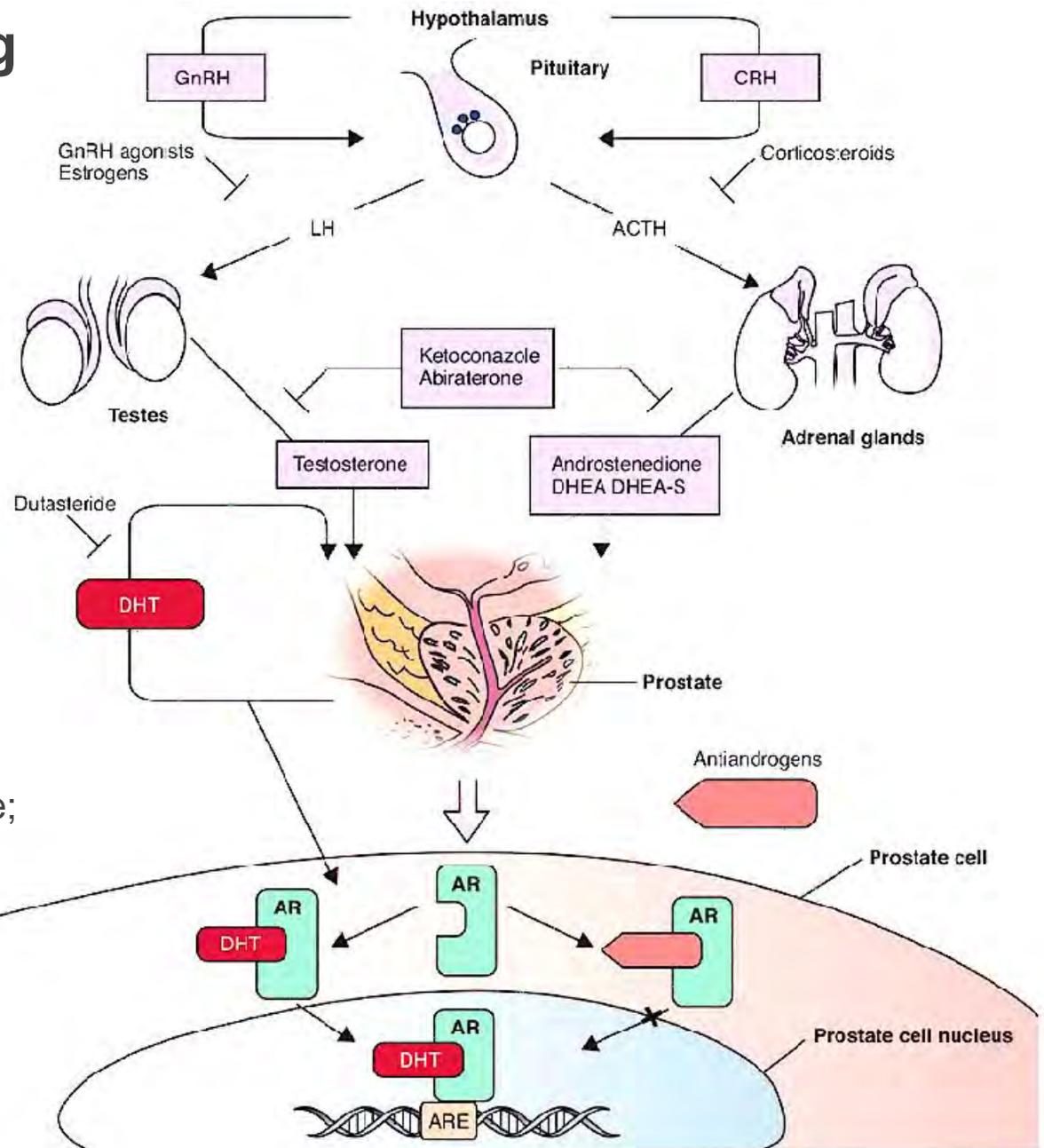
Treatment options for metastatic hormone sensitive cancer

- GnRH analogs (Leuprolide acetate, Goserelin acetate)
 - GnRH antagonists (Degarelix)
 - Anti androgens (Flutamide, Bicalutamide, Nilutamide)
 - Intermittent Androgen Deprivation Therapy(ADT)
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1 treatment options for patients with metastatic castration resistant disease

- GnRH analog plus Anti-androgen
 - Adrenal Suppressants (Ketoconazole + Hydrocortisone)
 - Androgen biosynthesis inhibitor (Abiraterone)
 - Immunotherapy (Sipuleucel-T)
 - Androgen receptor inhibitor (Enzalutamide)
 - Bone seeking radio isotopes (Radium-223)
 - Chemotherapy (Docetaxel, Cabazitaxel)
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The androgen-signaling axis and its inhibitors



GnRH, gonadotropin releasing hormone; LH, luteinizing hormone; CRH, corticotropin releasing hormone; ACTH, adrenocorticotrophic hormone; DHEA, dehydroepiandrosterone; DHEA-S, dehydroepiandrosterone sulphate; DHT, dihydrotestosterone; AR, androgen receptor; ARE, androgen response element

Purpose of study

- High Gleason score Prostate cancer (scores of 8-10) carries a poor prognosis compared to Gleason Score of 7 or less.
- Management of these patients is very challenging due to aggressive clinical course.
- There were no prior studies done specifically in this group of high Gleason score patients to look for prognostic impact of age at the time of diagnosis.

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- We selected an age cutoff of 55 years old based on Humphreys retrospective study published in 2013, which showed an age less than 55 as a poor prognostic factor in Prostate cancer.
- We are also looking for prognostic effect of primary grade of the tumor in this group of high Gleason score Prostate cancer patients.

Methods and Materials

- Single institution retrospective study
- Total No. of Patients: 89 from the year 2003 to 2015
- 34 and 55 patients aged ≤ 55 and > 55 years respectively
- 63 and 26 patients had primary grade of 4 and 5 respectively
- All patients:
 - Metastatic disease
 - High Gleason score
 - Treated with Androgen Deprivation Therapy
 - Had at least 6 months of follow up

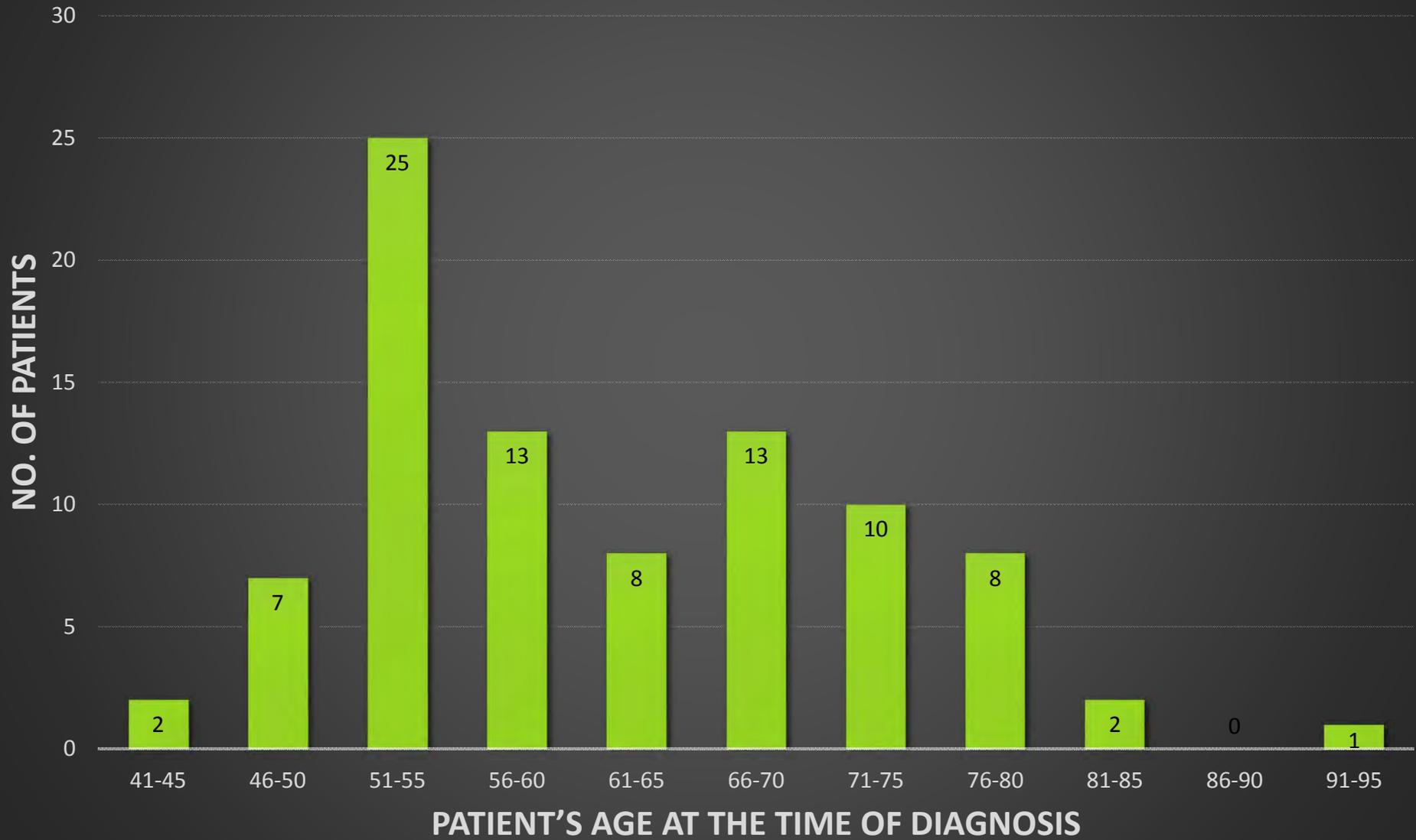
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- **Overall Survival** is defined as time from metastasis until last follow up or death and was analyzed using Kaplan-Meier method
 - **Progression free survival** is defined as time from start of the treatment until disease progression (biochemical & radiological) was analyzed for all treatments using Kaplan-Meier method
 - PSA progression was defined by PCWG2 criteria and radiological progression by RECIST criteria
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- Propensity scores were generated using logistic regression and were based on site of metastasis, PSA, race, ECOG, secondary grade and either age or primary grade
 - P-value less than 0.05 is considered statistically significant.
 - In terms of demographics, only significant finding is the difference in levels of hemoglobin (14.2 Vs 13.1) and alkaline phosphatase (90 Vs 120) between the primary grades of 4 and 5.
 - No differences were found between the two age groups.
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Age distribution



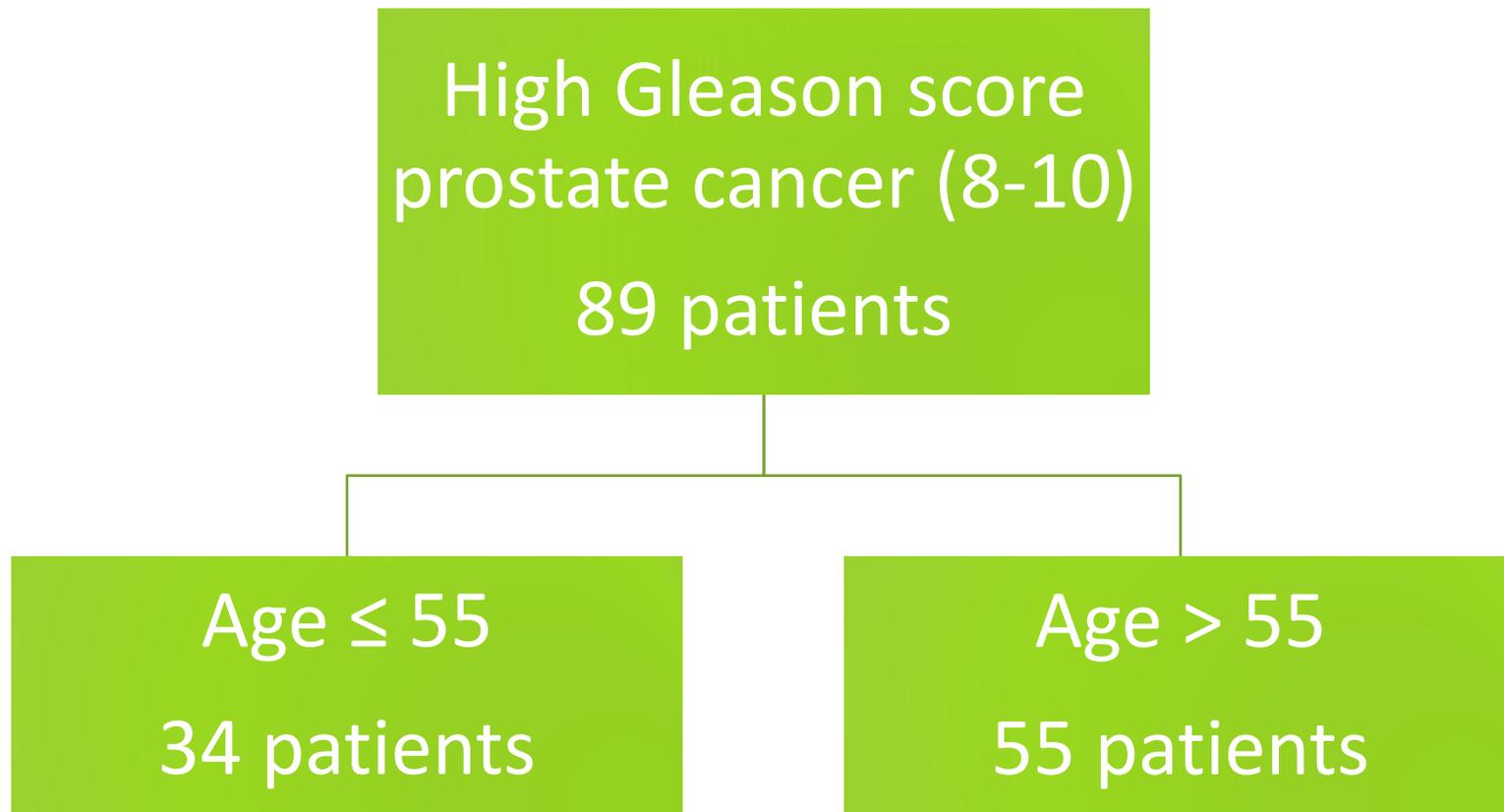
End Points

➤ **Primary end point:**

Survival difference between age groups of ≤ 55 and > 55 .

➤ **Secondary end point:**

Survival difference between primary grade of 4 and 5.



- Overall survival and Progression free survival difference

Overall survival

By age difference ≤ 55 Vs >55

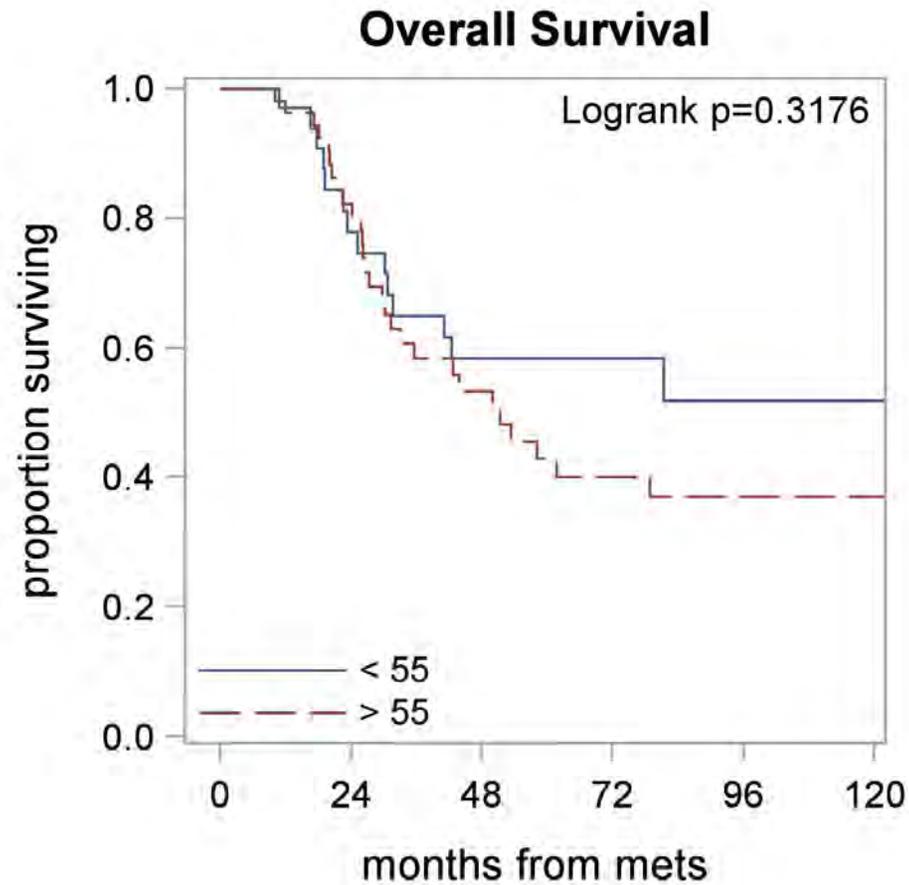
	1-yr Surv.Rate (95% CI)	3-yr Surv.Rate (95% CI)	Median Surv. (95% CI)	Median Follow-up (Range)	Sample
Total	0.97 (0.90, 0.99)	0.61 (0.49, 0.71)	58.1 (35.5, NR)	79.8 (7.5, 130.4)	E=42 C=47 T=89
≤ 55	0.97 (0.81, 1.00)	0.65 (0.46, 0.79)	NR (30.6, NR)	72.8 (13.4, 128.3)	E=14 C=20 T=34
>55	0.96 (0.86, 0.99)	0.58 (0.43, 0.71)	51.3 (30.2, NR)	83.8 (7.5, 130.4)	E=28 C=27 T=55

Propensity Analysis

Comparison	Hazard Ratio (95% CI)	P-value
>55 vs ≤ 55	1.370 (0.689, 2.725)	0.370

Overall survival

By age difference ≤ 55 Vs >55



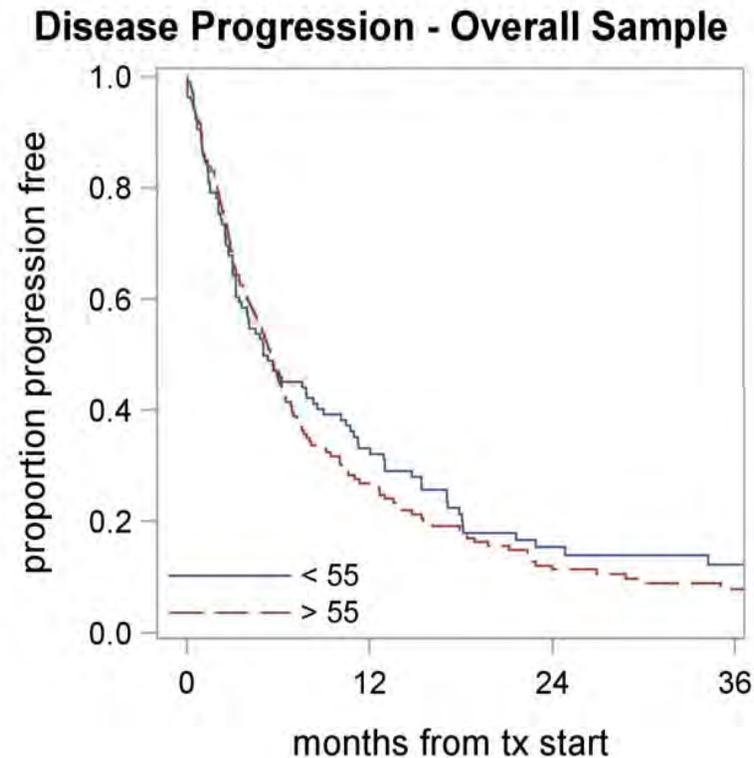
Progression free Survival By age difference ≤ 55 Vs >55

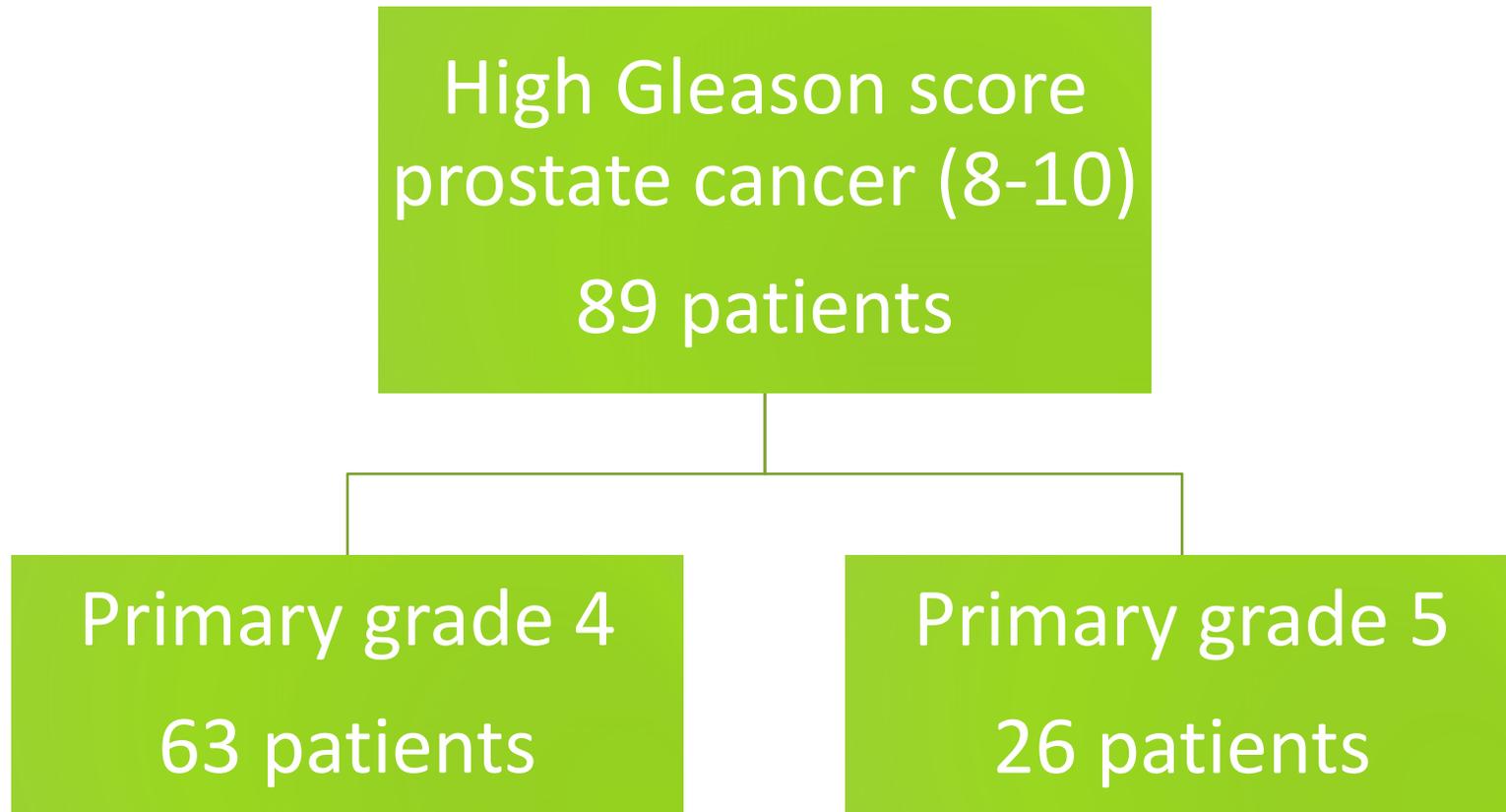
Cohort	Comparison	Hazard Ratio (95% CI)	P-value	Median PFS Age ≤ 55	Median PFS Age > 55
Overall Sample	≤ 55 versus >55	0.937 (0.719, 1.220)	0.627	5.75	5.29

Propensity Analysis

Cohort	Comparison	Adjusted Hazard Ratio (95% CI)	P-value
Overall Sample	≤ 55 versus >55	0.897 (0.681, 1.183)	0.442

Progression free Survival By age difference ≤ 55 Vs >55





- Overall survival and Progression free survival difference

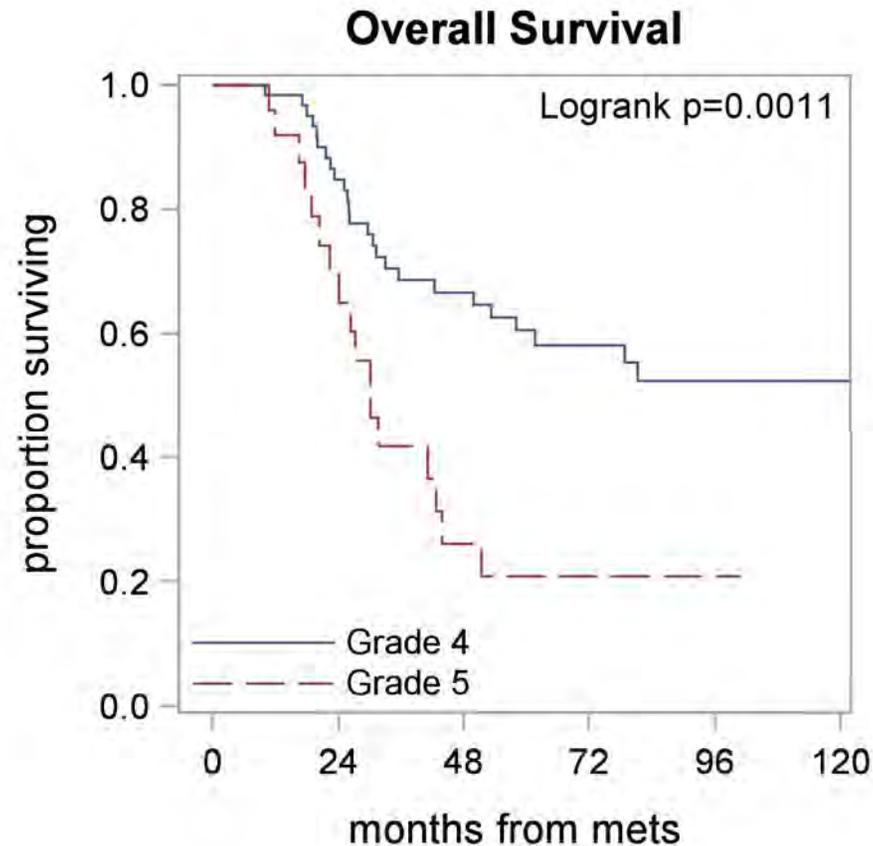
Overall survival difference By primary grade 4 Vs 5

	1-yr Surv.Rate (95% CI)	3-yr Surv.Rate (95% CI)	Median Surv. (95% CI)	Median Follow-up (Range)	Sample
Total	0.97 (0.90, 0.99)	0.61 (0.49, 0.71)	58.1 (35.5, NR)	79.8 (7.5, 130.4)	E=42 C=47 T=89
Grade 4	0.98 (0.89, 1.00)	0.69 (0.55, 0.79)	NR (53.4, NR)	83.8 (12.0, 130.4)	E=25 C=38 T=63
Grade 5	0.92 (0.72, 0.98)	0.42 (0.21, 0.61)	30.2 (22.5, 43.8)	64.2 (7.5, 101.0)	E=17 C=9 T=26

Propensity analysis

Comparison	Hazard Ratio (95% CI)	P-value
Grade 5 Vs Grade 4	2.088 (1.029, 4.238)	0.042

Overall survival difference By primary grade 4 Vs 5



Progression free survival difference

By primary grade 4 Vs 5

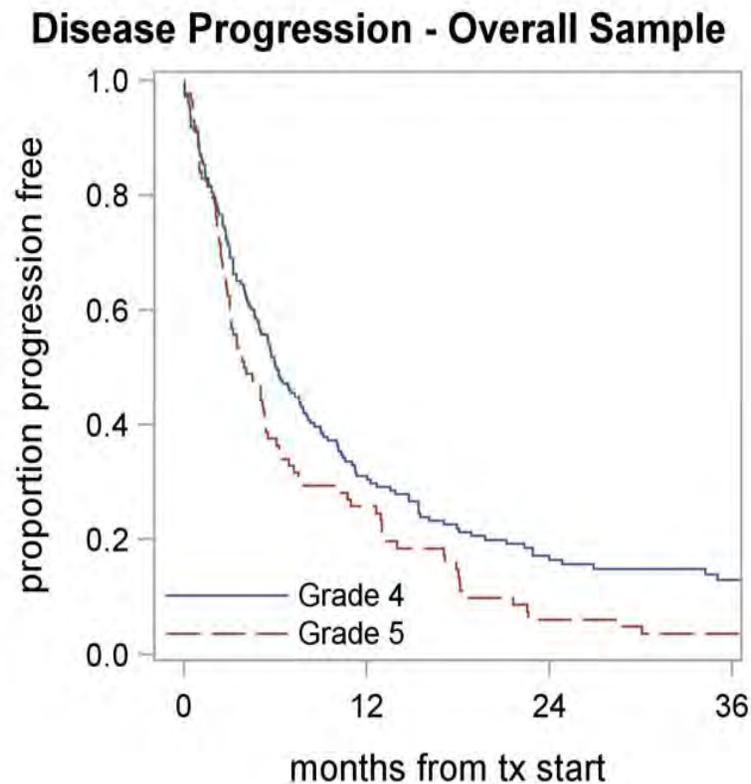
Cohort	Comparison	Hazard Ratio (95% CI)	P-value	Median PFS Grade 4	Median PFS Grade 5
Overall Sample	Grade 5 versus grade 4	1.432 (1.093, 1.878)	0.009	7.01	4.37

Propensity Analysis

Cohort	Comparison	Adjusted Hazard Ratio (95% CI)	P-value
Overall Sample	Grade 5 versus grade 4	1.398 (1.029, 1.898)	0.032



Progression free survival difference By primary grade 4 Vs 5



Summary of results

➤ **Age ≤ 55 Vs > 55 :**

No statistically significant difference was found in terms of overall survival (P-value: 0.3176)

No progression free survival difference was found on treatments (P-value: 0.627)

➤ **Primary grade 4 Vs 5:**

Overall survival was significantly shorter in primary grade of 5 (30.2 months Vs Not reached, P-value: 0.0011)

Shorter progression free survival on treatment in Primary grade of 5 (hazard ratio of 1.432, P-value: 0.009)

Conclusions

- In patients with high Gleason score Prostate cancer, age at diagnosis <55 years old is not a poor prognostic factor.
- Primary grade of 5 showed shorter overall survival and shorter progression free survival on treatments compared to primary grade of 4.
- In addition to the Gleason score, primary grade of 5 acts as an independent prognostic factor
- In patients with Gleason score of 9, it could mean that a histologic grade of 5+4 might be worse than 4+5 pattern reflecting the importance of primary grade of the tumor.

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- Hypothetically, a primary grade 5 metastatic Prostate cancer could be androgen independent or dependent on other signaling pathways
- So this group of patients might benefit from upfront chemotherapy/novel therapeutic agents in addition to hormonal therapy.

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- Dr. Kristopher Attwood, PhD, Roswell Park Cancer Institute

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Thank You

