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Trends in Initial Management of Prostate Cancer in New Hampshire

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ORIGINAL PAPER

Trends in initial management of prostate cancer in New Hampshire

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Abstract
Purpose Prostate cancer management strategies are evolving with increased understanding of the disease. Specifically, there is emerging evidence that "low-risk" cancer is best treated with observation, while localized "high-risk" cancer requires aggressive curative therapy. In this study, we evaluated trends in management of prostate cancer in New Hampshire to determine adherence to evidence-based practice.
Methods From the New Hampshire State Cancer Registry, cases of clinically localized prostate cancer diagnosed in 2004–2011 were identified and classified according to D'Amico criteria. Initial treatment modality was recorded as surgery, radiation therapy, expectant management, or hormone therapy. Temporal trends were assessed by Chi-square for trend.
Results Of 6,203 clinically localized prostate cancers meeting inclusion criteria, 34, 30, and 28 % were low-, intermediate-, and high-risk disease, respectively. For low-risk disease, use of expectant management (17–42 %, $p < 0.001$) and surgery (29–39 %, $p < 0.001$) increased, while use of radiation therapy decreased (49–19 %, $p < 0.001$). For intermediate-risk disease, use of surgery increased (24–50 %, $p < 0.001$), while radiation decreased (58–34 %, $p < 0.001$). Hormonal therapy alone was rarely used for low- and intermediate-risk disease. For high-risk patients, surgery increased (38–47 %, $p = 0.003$) and radiation decreased (41–38 %, $p = 0.026$), while hormonal therapy and expectant management remained stable.
Discussion There are encouraging trends in the management of clinically localized prostate cancer in New Hampshire, including less aggressive treatment of low-risk cancer and increasing surgical treatment of high-risk disease.

Keywords Prostate cancer · Management trends · Risk stratification · Active surveillance · Surgery

Introduction

Prostate cancer is the most common cancer diagnosis in men in the USA, with ~220,000 new diagnosis projected in 2015. While most prostate cancer is slow-growing and non-lethal, a subset of cancers will become metastatic and cause mortality (~28,000 men in 2015) [1]. A newly diagnosed cancer is categorized as "low," "intermediate," or "high risk" based on biopsy findings, prostate-specific antigen (PSA) level, and physical examination findings (presence or absence of prostate nodularity) [2]. This risk category reflects the likelihood of progression and lethality and is used for making treatment decisions in conjunction with patient age, health status, and other concerns such as sexual and urinary function.

Longitudinal data have demonstrated a high rate of treatment for all risk categories [3]. While aggressive treatment in the form of surgery or radiation therapy is

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appropriate for more aggressive cancers, "low-risk" disease can often be safely observed, and patients can be spared the side effects of treatment. There are emerging data that "expectant management," including active surveillance (with follow-up biopsy) and watchful waiting (with monitoring based on symptoms only), is safe and associated with a low risk of cancer mortality for appropriate low-risk patients. In fact, a study with a follow-up time of 18 years found that patients with low-risk cancer were far more likely to die from causes other than prostate cancer [4]. These approaches have been incorporated into recent treatment guidelines by the American Urological Association, European Association of Urology, and the National Comprehensive Cancer Network [6–8]. Nonetheless, there continues to be a high rate of aggressive treatment of low-risk cancer, incurring treatment morbidity without a concomitant survival benefit [5].

"High-risk" prostate cancer presents the opposite challenge—many patients are treated with non-curative therapies such as testosterone suppression or "hormone therapy," when they might benefit from aggressive local treatment with radiation or surgery [9, 10]. This has presented a quality of care concern [11]. Additionally, while radiation therapy has been used more commonly for treatment of high-risk disease, studies have demonstrated similar long-term outcomes between radiation therapy and radical prostatectomy, with a suggestion of a benefit from surgery for selected patients [12, 13] Ultimately, there are multiple treatment options for all risk categories, and thus treatment decisions are often considered "preference-sensitive" and emerge from a nuanced conversation between provider and patient [14, 15].

In this paper, we examined trends in the management of localized prostate cancer in New Hampshire using state cancer registry data. We sought to evaluate whether statewide practices are consistent with our growing understanding of prostate cancer behavior and potential optimal therapies (i.e., increasing use of expectant management for low-risk cancer and definitive therapy for higher-risk cancer).

Materials and methods

Clinically localized (non-metastatic) prostate cancers diagnosed from 2004 to 2011 were identified in the New Hampshire State Cancer Registry (NHSCR). NHSCR is a statewide, population-based cancer surveillance program that collects incidence data on all cancer cases diagnosed or treated in New Hampshire residents, including clinical data such as stage, a preoperative Gleason grade on a transrectal biopsy or a transurethral resection specimen, PSA, and initial treatment. Clinically localized disease was defined as AJCC 7th Edition T Stage 1–2. Cases were excluded for the following reasons: cancer confirmation only by death certificates, autopsy, or pathology or nursing home records; patients diagnosed and treated by the Veterans Health Adminstration due to restrictions in data use; evidence of lymph node involvement, N1, or metastasis, M1; unclassified D'Amico risk category due to missing or unconfirmed preoperative data. The study period was initiated in 2004 as this is the first year in which complete data were recorded, including preoperative PSA, clinical stage, and biopsy Gleason score. 2011 was the most recent year with complete information.

Cancers were stratified according to D'Amico risk categories. Men with PSA <10, biopsy Gleason score 6, clinical stage T1c, and/or clinical stage T2a were classified as low risk, men with PSA 10–20, biopsy Gleason score 7, and/or clinical stage T2b as intermediate risk, and men with PSA >20, biopsy Gleason score 8+, and/or clinical stage T2c+ as high risk [2]. The initial treatment was recorded as surgical therapy, radiation (external beam radiotherapy and/or brachytherapy), primary androgen deprivation (ADT) therapy (men on ADT plus radiation were counted as initial radiation therapy), or expectant management (no therapy recorded within 6 months). The data from the cancer registry were not granular enough to differentiate "active surveillance" (monitoring with follow-up biopsy) from "watchful waiting" (symptomatic monitoring only). Subsequent treatment was not recorded in our analysis as our goal was to study initial therapy rather than adjuvant or salvage therapies. Men who underwent subsequent treatment by another modality were not excluded, however.

Temporal trends were assessed by Chi-square for trend, with a p value of <0.05 considered significant. This investigation was approved by the Dartmouth Committee for the Protection of Human Subjects, and data use was approved by the New Hampshire Department of Public Health Services.

Results

Of the 7,706 potentially eligible cases, 1,062 were excluded because the preoperative D'Amico risk category could not be calculated due to a missing biopsy Gleason score or an uncertain source (biopsy vs. surgical pathology). A further 441 were excluded because the D'Amico risk category was unknown due to other missing data. The remaining 6,203 men had clinically localized prostate cancer and met the inclusion criteria. Demographics are shown in Table 1. The mean age was 65.7 ± 9.3 years. There was an average annual increase in diagnosis of 2.2 %, matching population growth among men over the

Table 1 Population demographics

	Low risk ($n = 2,302$)		Intermediate risk ($n = 1,997$)		High risk ($n = 1,904$)		All cases ($n = 6,203$)		χ^2
	No.	%	No.	%	No.	%	No.	%	
Age									0.000
<50	84	3.6	33	1.7	34	1.8	151	2.4	
50–65	1,249	54.3	910	45.6	780	41.0	2,939	47.4	
66–75	808	35.1	768	38.5	703	36.9	2,279	36.7	
>75	161	7.0	286	14.3	387	20.3	834	13.4	
Mean, SD	63.6, 8.1		66.11, 8.4		67.4, 9.4		65.6, 8.8		
Residence[a]									0.000
Rural	902	39.3	905	45.4	903	47.6	2,710	43.8	
Urban	1,393	60.7	1,087	54.6	995	52.4	3,475	56.2	
Marital status									0.000
Single	174	7.6	150	7.5	139	7.3	463	7.5	
Married/common law	1,811	78.7	1,561	78.2	1,416	74.4	4,788	77.2	
Divorced/separated	164	7.1	145	7.3	135	7.1	444	7.2	
Widowed	76	3.3	84	4.2	116	6.1	276	4.4	
Unknown	77	3.3	57	2.9	98	5.1	232	3.7	
Calendar year									0.000
2004	239	10.4	143	7.2	256	13.4	642	10.4	
2005	211	9.2	155	7.8	224	11.8	593	9.6	
2006	256	11.1	214	10.7	239	12.6	710	11.4	
2007	282	12.3	264	13.2	246	12.9	792	12.8	
2008	310	13.5	307	15.4	233	12.2	848	13.7	
2009	294	12.8	294	14.8	242	12.8	830	13.4	
2010	370	16.0	290	14.5	235	12.3	893	14.4	
2011	340	14.8	330	16.5	228	12.0	894	14.4	
PSA lab value									0.000
<10	2,302	100.0	1,595	79.9	1,080	56.7	4,977	80.2	
10 to <20	0	0.0	402	20.1	235	12.3	637	10.3	
20+	0	0.0	0	0.0	498	26.2	498	8.0	
Test ordered, result not in chart	0	0.0	0	0.0	5	0.3	5	0.1	
Test not done	0	0.0	0	0.0	8	0.4	8	0.1	
Unknown if done	0	0.0	0	0.0	78	4.1	78	1.3	
Biopsy Gleason score							0.000		
≤6	2,302	100.0	234	11.7	478	25.1	3,014	48.6	
7	0	0.0	1,763	88.3	551	28.9	2,314	37.3	
8–10	0	0.0	0	0.0	864	45.4	864	13.9	
No BX/TURP performed	0	0.0	0	0.0	4	0.2	4	0.1	
Unknown if test done	0	0.0	0	0.0	7	0.4	7	0.1	
AJCC cT									0.000
1	1,871	81.3	1,442	72.2	582	30.6	3,895	62.8	
2a	254	11.0	255	12.8	100	5.3	609	9.8	
2b	0	0.0	162	8.1	71	3.7	233	3.8	
2c+	0	0.0	0	0.0	1,018	53.5	1,018	16.4	
2NOS	177	7.7	138	6.9	104	5.5	419	6.8	
Unknown	0	0.0	0	0.0	29	1.5	29	0.5	

[a] 5 zip codes in New Hampshire have not been classified as either rural or urban, leading to a smaller *n*

age of 65 in New Hampshire. There was a shift in the age of diagnosed patients during the study period; 46 % of patients were under 65 years of age in 2004 but 56 % in 2011. Similarly, 16 % of diagnosed men were older than 75 in 2004, but 11 % in 2011. Diagnoses were similarly distributed within calendar years. Overall, 2,302 (34 %), 1,997 (30 %), and 1,904 (28 %) men were diagnosed with low-, intermediate-, and high-risk disease, respectively. There was a proportional decrease in high-risk disease (39–27 % of all cancer diagnosis, $p < 0.001$) and increase in intermediate disease (26–36 %, $p < 0.001$). Shifts in low-risk cancer diagnosis did not reach significance. Overall, there was an increase in use of surgery and expectant management as first treatment choice, and a decrease in radiation and primary androgen deprivation (see Fig. 1), although patterns varied by D'Amico risk category.

Figure 2 depicts trends of initial treatments for patients with low-risk disease. Use of expectant management more than doubled (17–42 %) during the study period. Surgery was also performed more often (29–39 %). The use of initial radiation therapy decreased significantly (49–19 %), as did treatment with initial androgen deprivation (5–0.3 %).

For intermediate-risk patients, surgery rates doubled (24–50 %), while radiation (58–34 %) and primary hormonal deprivation decreased (9–3 %) as shown in Fig. 3. There was no statistically significant change in use of expectant management, which was used in 13 % of cases.

Among patients with high-risk disease, surgery and radiation were each used as initial treatment in about 40 % of the cases with fluctuations between years as shown in Fig. 4. There was, however, a statistically significant trend toward increased surgical treatment (38–47 %, $p = 0.003$) and a decrease in radiation therapy (41–38 %, $p = 0.026$). The changes in hormonal therapy and expectant management did not display a statistically significant trend.

The median age of men in each treatment group was 60.4 ± 6.9 for surgery, 68.8 ± 7.2 for radiation, 68.9 ± 9.4 for expectant management, and 73.2 ± 8.6 for initial hormonal therapy.

Discussion

Prostate cancer is a common disease that is generally non-lethal; however, it can also behave aggressively leading to metastasis and death. Initial "risk categorization" based on laboratory, biopsy, and physical examination data reflects the likelihood of an adverse outcome and helps to inform decisions regarding treatment [1]. Surgery (radical prostatectomy) and radiation therapy (external beam therapy and/or radioactive seed therapy) are first-line interventions for localized prostate cancer [6]. Notably, there have been no prospective, randomized trials comparing surgery and radiation in this setting; data regarding comparative effectiveness are limited to retrospective, matched cohort trials that cannot avoid selection bias [2, 16, 17]. Thus, absent level 1 evidence favoring one therapy, decisions for those pursuing treatment frequently depend on patient and provider preferences and resource availability [14, 15]. An alternative strategy for management of localized cancer is observation. This is particularly considered for low-risk disease, as it has a low risk of progression, and patients will generally die from another cause [18, 19]. As surgery and radiation therapy have well-described morbidity (e.g., erectile, urinary, and/or bowel dysfunction), monitoring a low-risk cancer is often a sensible approach to balance risks and benefits, and to optimize quality of life [20]. Finally, hormone therapy alone, also called androgen deprivation therapy (ADT), is a treatment for metastatic cancer that can reduce morbidity but has not been shown to improve survival, and is considered inappropriate as singular therapy in cases of localized disease [6–8].

We performed this study to evaluate trends in management of localized prostate cancer in New Hampshire and to understand whether they reflect our growing understanding

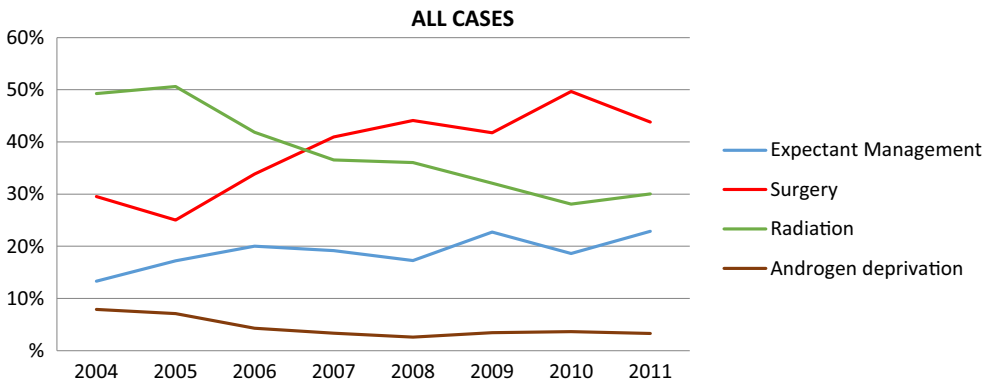

Fig. 1 Changes in initial treatment modality for clinically localized prostate cancer by calendar year. Trends are statistically significant with a p value <0.001 for all treatment modalities

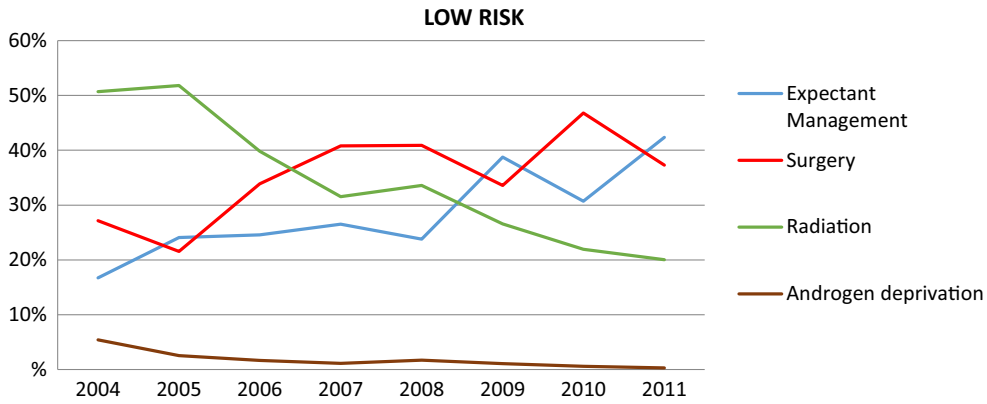

Fig. 2 Changes in initial treatment modality for D'Amico low risk clinically localized prostate cancer by calendar year. Trends are statistically significant with a p value <0.001 for all treatment modalities

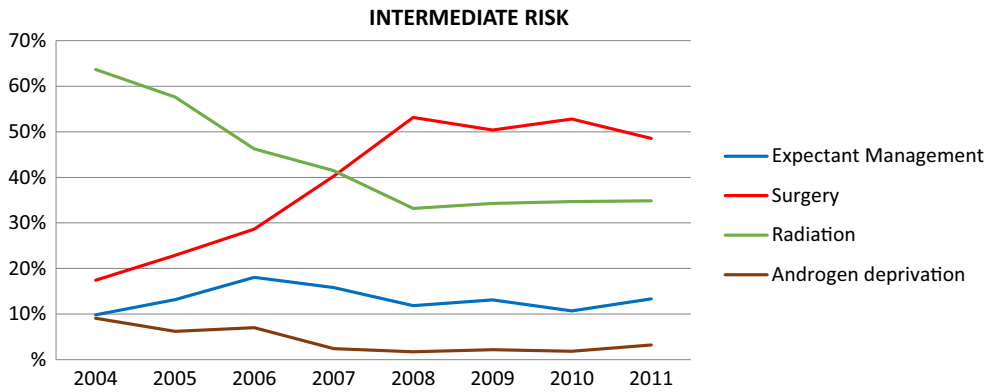

Fig. 3 Changes in initial treatment modality for D'Amico intermediate risk clinically localized prostate cancer by calendar year. Trends are statistically significant with a p value <0.001 for surgery, radiation and androgen deprivation

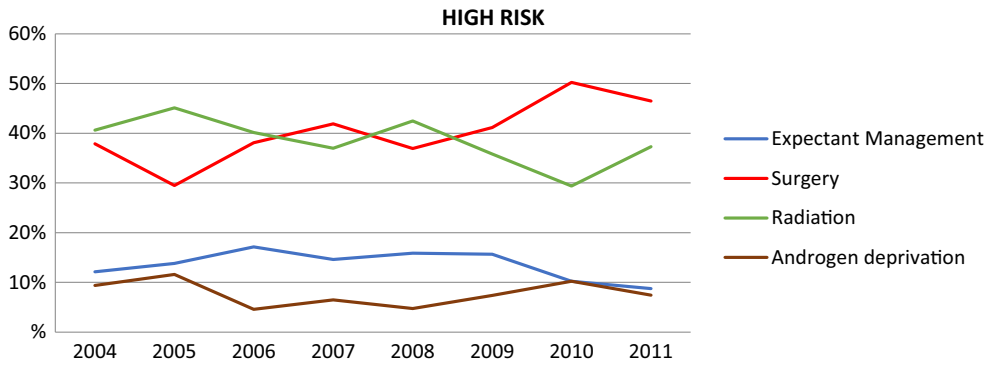

Fig. 4 Changes in initial treatment modality for D'Amico intermediate risk clinically localized prostate cancer by calendar year. Trends are statistically significant with for surgery ($p = 0.003$) and radiation ($p = 0.026$)

of appropriate practice. We demonstrated several findings that are encouraging regarding the quality of treatment. Perhaps most importantly, we found that observation or an "expectant management" strategy has become increasingly common as first-line treatment for low-risk disease. These trends reflect emerging data from observational studies that such strategies are safe and appropriate for most low-risk patients [20]. A study by Weiner et al. [21] recently examined the utilization of non-curative initial management in the Surveillance, Epidemiology and End Result Program (SEER) and National Cancer Data Base (NCDB). These authors also found a significant rise in expectant management for low-risk cancer (SEER 20–31 %, NCDB 12–21 % from 2004 to 2010); however, the shift toward this approach in New Hampshire was more dramatic (18–42 % from 2004 to 2011). New Hampshire is largely a rural state; however, there are regional referral centers where most patients are treated. Thus, we postulate that consolidation of care at certain centers has led to more rapid uptake of expectant management for low-risk disease. The New Hampshire State Cancer Registry collects the same core set of variables as other national registries such as SEER or NCDB, and it resembles SEER in that it produces population-based data. NCDB, however, does not

produce population-based statistics but collects data from hospitals that are accredited by the American College of Surgeons Commission on cancer.

Despite these encouraging trends, our data also demonstrate that the overall treatment rate for low-risk cancer is high (>50 % in 2011). While this likely reflects continued overtreatment of many patients, it is notable that selected cases of low-risk cancer should be treated aggressively, e.g., patients with high-volume disease, family history of early mortality from prostate cancer, and significant anxiety associated with the monitoring process. Additional studies are needed to determine whether patients with low-risk cancer are being appropriately selected for treatment, and how to further encourage observational strategies to reduce overtreatment.

Interestingly, our data demonstrate increasing use of surgical treatment for low-risk cancer with a parallel decrease in radiation therapy. Reasons for this "exchange" of interventions are unclear, though the advent of less invasive forms of prostatectomy (i.e., robotic surgery), which was introduced to New Hampshire during the study period, may contribute. For intermediate-risk cancer, trends demonstrate a similar rise in use of surgery with a decrease in radiation therapy. For this risk category, treatment is recommended for most patients, provided they do not have a significantly shortened life expectancy, though there are no strict guidelines favoring surgery or radiation therapy [22]. The rise in use of surgical therapy likely reflects diverse factors that cannot be captured in this study, though this is a ripe area of study to determine factors influencing treatment decisions for these patients.

For high-risk cancer, we demonstrate a significant increase in the use of surgical therapy, with a slight decrease in use of radiation. While radiation therapy has been the historical default treatment option for clinically localized high-risk disease, surgical treatment has been increasingly considered as a primary treatment. Data have emerged that surgery may achieve cure with wide surgical resection and pelvic lymph node removal, as well as a favorable outcome when used in concert with adjuvant or salvage radiation and hormone therapy [23]. In the contemporary treatment arena, it is critical that surgery be discussed with and contemplated by those with localized high-risk cancer, as it may better meet patient preferences than primary radiation therapy. Thus, it is encouraging that aggressive local therapy with surgery alone, or as a starting point for a multimodal approach, is being offered to patients with high-risk cancer. Finally, we found a low, stable rate of hormone monotherapy for high-risk cancer. This is encouraging, as hormone therapy lacks a survival benefit for clinically localized disease, may have significant side effects, and has been shown to be overused in the treatment of these patients [9, 10].

There are numerous variables that may affect treatment choices for prostate cancer, including screening patterns and stage migration. Studies have demonstrated a decrease in rates of screening, particularly in older patients, after the 2008 United States Preventive Services Task Force recommendations [24]. While our data did not incorporate screening practices, we did find no decrease in overall cancer rates during the study period, though there were some shifts in risk categories; specifically, more intermediate-risk and fewer higher-risk cancers were identified. While these changes may impact overall treatment trends, we report treatment decisions within risk categories which make these changes less relevant. In terms of demographic shifts, there were fewer diagnoses in older men during our study period, however, this change was small and we do not believe this significantly impacted treatment decisions.

There are some limitations of our study that warrant discussion. The registry data did not contain comorbidity data that might be used to assess competing risks of death and how these might impact treatment practices. As such, we were only able to capture trends in treatment without assessing potential medical confounders. Also, while the data collected by NHSCR are of high quality, 19.5 % of eligible cases were excluded due to missing clinical data. It is important, though, to interpret this number in light of our strict inclusion criteria that required clinical stage, PSA, and biopsy Gleason score for accurate categorization. We could not assess differences in disease risk between included and excluded patients because the latter, by definition, had incomplete data.

Another limitation of our study is our definition of "expectant management" as those with no intervention within 6 months of diagnosis. This is the conventional definition used in the literature for population-based studies, though it may include some patients who had delayed treatment but nonetheless had planned on a definitive intervention, for instance, in the 6- to 12-month window. Finally, our data represent practice within a largely rural state and may not be generalizable to other regions. In particular, travel distances and extreme winter weather may influence treatment decisions, especially when multiple trips for treatment would be required [25]. We are currently evaluating the impact of distant to a radiation facility on treatment decisions and hope to report this in a future manuscript.

Conclusion

There are encouraging trends in the management of clinically localized prostate cancer in New Hampshire, including increased observation of low-risk cancer, and increasing surgical treatment of high-risk disease. Continued

efforts to study and refine practice patterns will enable us to optimize our approaches to this heterogeneous disease.

Conflict of interest The authors declare that they have no conflicts of interest.

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