1. Introduction

The European Association of Urology (EAU) Guidelines Group on Muscle-Invasive and Metastatic Bladder Cancer prepared these guidelines to deliver current evidence-based information on the diagnosis and treatment of patients with primary urethral carcinoma (UC). When the first carcinoma in the urinary tract is detected in the urethra, it is defined as primary urethral carcinoma (UC). The European Association of Urology (EAU) Guidelines Group on Muscle-Invasive and Metastatic Bladder Cancer prepared these guidelines to deliver current evidence-based information on the diagnosis and treatment of patients with primary urethral carcinoma (UC). When the first carcinoma in the urinary tract is detected in the urethra, it is defined as primary urethral carcinoma (UC).
primary UC, in contrast to secondary UC, which presents as a recurrent carcinoma in the urethra after prior diagnosis and treatment of carcinoma elsewhere in the urinary tract. Most often, secondary UC is reported after radical cystectomy for bladder cancer [1] (see Chapter 14 of the EAU guidelines on muscle-invasive and metastatic bladder cancer [2]).

2. Methodology

A systematic literature search was performed to identify studies reporting urethral malignancies. Medline was searched using the controlled vocabulary of the Medical Subject Headings database, along with a free-text protocol, using one or several combinations of the following terms: adenocarcinoma, adjuvant treatment, anterior, chemotherapy, distal urethral carcinoma, lower, neoadjuvant, partial, penectomy, penile-preserving surgery, posterior, primary, proximal urethral carcinoma, radiotherapy, recurrence, risk factors, squamous cell carcinoma, survival, transitional cell carcinoma, urethra, urethrectomy, urethral cancer, urinary tract, and urothelial carcinoma. No randomised controlled trials were identified, and articles were selected based on study design, treatment modality, and long-term outcomes. Older studies (>10 yr) were considered if they contained historically relevant data or in the absence of newer data.

3. Level of evidence and grade of recommendation

References in the text were assessed according to their level of evidence (LE), and a grade of recommendation (GR) was assigned according to the lists in Tables 1 and 2, based on the Oxford Centre for Evidence-based Medicine levels of evidence [3]. Grading aims to provide transparency between the underlying evidence and the recommendation given [3]. Because primary UC belongs to the family of rare cancers, most studies are retrospective, and recommendations given in these guidelines are mainly based on level 3 evidence.

4. Epidemiology

Primary UC is considered a rare cancer, accounting for <1% of all malignancies [4] (International Classification of Diseases for Oncology, 3rd edition, topography code C68.0 [5]).

The RARECARE project, set up to describe the epidemiology of rare urogenital cancers in 64 European population-based cancer registries (covering 32% of the population of the 27 member states of the European Union, reported recently on 1059 new cases of epithelial urethral tumours detected between 1995 and 2002 [6]. In early 2008, the prevalence of UC in the 27 EU countries was 4292 cases with an estimated annual incidence of 655 new cases. The age-standardised ratio was 1.1 per million inhabitants (1.6 per million in men and 0.6 per million in women, a male-to-female ratio of 2.9) [6]. There were differences between European regions potentially caused by registration or classification [6]. In an analysis of the Surveillance Epidemiology and End Results (SEER) database, the incidence of primary UC peaked in the >75 yr age group (7.6 per million). The age-standardised rate was 4.3 per million in men and 1.5 per million in women, and UC was almost negligible in those <55 yr of age (0.2 per million) [7].

5. Aetiology and risk factors

For male primary UC, various predisposing factors have been reported including urethral strictures [8,9], chronic irritation after intermittent catheterisation/urethroplasty [10–12], external-beam radiation therapy [13], radioactive seed implantation [14], and chronic urethral inflammation/urethritis following sexually transmitted diseases (ie, condylomata associated with human papillomavirus 16) [15,16]. In female UC, urethral diverticula [17–19] and recurrent urinary tract infections [20] are associated with primary carcinoma. Clear cell adenocarcinoma may also have a congenital origin [21].

6. Histopathology

Both the RARECARE project and SEER database reported that urothelial carcinoma of the urethra is the predominant histologic type of primary UC (54–65%), followed by squamous cell carcinoma (SCC; 16–22%) and adenocarcinoma (AC; 10–16%) [6,7]. A recent SEER analysis of 2065 men with primary UC (mean age: 73 yr) found that urothelial carcinoma (78%) was most common, and SCC (12%) and AC (5%) were significantly less frequent [22]. In women, a recent report of the National Cancer Registry of
the Netherlands on primary UC reported that urothelial carcinoma occurred in 45% of cases, followed by AC in 29%, SCC in 19%, and other histologic entities in 6% [23]. Several other rare histologic types of urethral malignancies were also described in these studies.

7. **Classification**

7.1. **TNM staging system**

In men and women, UC is classified according to the 7th edition of the TNM classification [5] (Table 3). It should be noted that there is a separate TNM staging system for prostatic UC [5]. Notably, for cancers occurring in the urethral diverticulum, stage T2 is not applicable because urethral diverticula are lacking periurethral muscle [24].

7.2. **Tumour grade**

The former World Health Organisation (WHO) grading system of 1973 that differentiates urothelial carcinomas into three different grades (G1–G3) was replaced by the grading system of 2004 that differentiates urothelial UC into papillary urothelial neoplasm of low malignant potential, low grade and high grade. Nonurothelial UC is graded by a trinomial system that differentiates between well-differentiated (G1), moderately differentiated (G2), and poorly differentiated (G3) tumours. Table 4 lists the different grading systems according to the WHO 1973 and 2004 systems [25].

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### Table 3 – TNM classification (7th edition) for urethral carcinoma [5]

<table>
<thead>
<tr>
<th>T</th>
<th>Primary tumour (men and women)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tx</td>
<td>Primary tumour cannot be assessed</td>
</tr>
<tr>
<td>Tis</td>
<td>Carcinoma in situ</td>
</tr>
<tr>
<td>T0</td>
<td>No evidence of primary tumour</td>
</tr>
<tr>
<td>Ta</td>
<td>Noninvasive papillary carcinoma</td>
</tr>
<tr>
<td>T1</td>
<td>Tumour invades subepithelial connective tissue</td>
</tr>
<tr>
<td>T2</td>
<td>Tumour invades any of the following structures: corpus spongiosum, prostate, periurethral muscle</td>
</tr>
<tr>
<td>T3</td>
<td>Tumour invades any of the following structures: corpus cavernosum, invasion beyond prostatic capsule, anterior vaginal wall, bladder neck</td>
</tr>
<tr>
<td>T4</td>
<td>Tumour invades other adjacent organs</td>
</tr>
</tbody>
</table>

**Primary tumour in prostatic urethra**

| T  | Primary tumour cannot be assessed |
| Tis pu | Carcinoma in situ in the prostatic urethra |
| Tis pd | Carcinoma in situ in the prostatic ducts |
| T0 | No evidence of primary tumour |
| T1 | Tumour invades subepithelial connective tissue (only in case of concomitant prostatic urethral involvement) |
| T2 | Tumour invades any of the following structures: corpus spongiosum, prostatic stroma, periurethral muscle |
| T3 | Tumour invades any of the following structures: corpus cavernosum, beyond prostatic capsule, bladder neck |
| T4 | Tumour invades other adjacent organs |

**N – Regional lymph nodes**

| N  | Regional lymph nodes cannot be assessed |
| N0 | No regional lymph node metastases |
| N1 | Metastasis in a single lymph node ≤ 2 cm in greatest dimension |
| N2 | Metastasis in a single lymph node > 2 cm in greatest dimension or in multiple nodes |

**M – Distant metastasis**

| M  | Distant metastasis cannot be assessed |
| M0 | No distant metastasis |
| M1 | Distant metastasis |

Primary tumour stage is separated into urethral carcinoma (UC) and UC of the prostate.

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### Table 4 – Histopathologic grading of urothelial and nonurothelial primary urethral carcinoma [25]

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>PUNLMP</td>
<td>Papillary urothelial neoplasm of low malignant potential</td>
</tr>
<tr>
<td>Low grade</td>
<td>Well differentiated</td>
</tr>
<tr>
<td>High grade</td>
<td>Poorly differentiated</td>
</tr>
</tbody>
</table>

**Nonurothelial urethral carcinoma**

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gx</td>
<td>Tumour grade not assessable</td>
</tr>
<tr>
<td>G1</td>
<td>Well differentiated</td>
</tr>
<tr>
<td>G2</td>
<td>Moderately differentiated</td>
</tr>
<tr>
<td>G3</td>
<td>Poorly differentiated</td>
</tr>
</tbody>
</table>
Pathologic staging and grading of primary UC should follow the 2009 TNM classification and WHO 2004 grading system.

8. Survival

8.1. Long-term survival after primary urethral carcinoma

According to the RARECARE project, the mean 1- and 5-yr overall survival in patients with UC in Europe is 71% and 54%, respectively [6]. With longer follow-up, a SEER analysis of 1615 cases reported median 5- and 10-yr overall survival rates of 46% and 29%, respectively. Cancer-specific survival at 5 and 10 yr was 68% and 60%, respectively [7].

8.2. Predictors of survival in primary urethral carcinoma

In Europe, mean 5-yr overall survival does not substantially differ between the sexes [6]. Predictors of decreased survival in patients with primary UC are as follows:

- Advanced age and race (≥65 yr) [6,26]
- Stage, grade, nodal involvement, and metastasis [22]
- Tumour size and proximal tumour location [22]
- Extent of surgical treatment and treatment modality [22,26]
- Underlying histology [6,23,26]

Some limitations must be taken into account in the interpretation of these results. In the Dutch study, the numbers were low (n = 91) [23]. In the large SEER database (n = 2046), therapy is not well specified in relation to survival [22]. Finally, in contrast to the RARECARE project [6], the opposite findings were reported in the SEER database in relation to the role of histology on survival in male patients [26].

8.3. Conclusion

Risk factors for survival in primary UC are age, tumour stage and grade, nodal stage, presence of distant metastasis, histologic type, tumour size, tumour location, and type and modality of treatment (LE: 3).

9. Diagnosis and staging

9.1. History

When becoming clinically apparent, most patients (45–57%) with primary UC present with symptoms associated with locally advanced disease (T3/T4) [23,27]. At initial presentation, visible haematuria or bloody urethral discharge is reported in up to 62% of the cases. Further symptoms of locally advanced disease include an extraurethral mass (52%), bladder outlet obstruction (48%), pelvic pain (33%), urethrocutaneous fistula (10%), abscess formation (5%), or dyspareunia [27].

9.2. Clinical examination

In men, physical examination should comprise palpation of the external genitalia for suspicious indurations or masses and a digital rectal examination [28]. In women, further pelvic examination with careful inspection and palpation of the urethra should be performed, especially in those with primary onset of irritative or obstructive voiding. In addition, bimanual examination, when necessary under general anaesthesia, should be performed for local clinical staging and to exclude the presence of colorectal or gynaecologic malignancies.

Bilateral inguinal palpation should be conducted to assess the presence of enlarged lymph nodes, describing location, size, and mobility [29].

9.3. Urinary cytology

The role of urinary cytology in primary UC is limited, and its sensitivity ranges between 55% and 59% [30]. Detection rate depends on the underlying histologic entity. In male patients, the sensitivity for urothelial carcinoma and SCC was reported to be 80% and 50%, respectively, whereas in female patients sensitivity was found to be 77% for SCC and 50% for urothelial carcinoma.

9.4. Diagnostic urethrocystoscopy and biopsy

Diagnostic urethrocystoscopy and biopsy enables primary assessment of a urethral tumour in terms of tumour extent, location, and underlying histology [28]. To enable accurate pathologic assessment of surgical margins, biopsy sites (proximal/distal end) should be marked and sent together with clinical information to the pathologist. Careful cystoscopic examination is necessary to exclude the presence of concomitant bladder tumours [2]. A cold-cut biopsy enables accurate tissue retrieval for histologic analysis and avoids artificial tissue damage. In patients with larger lesions, transurethral resection (optionally in men under penile blood arrest using a tourniquet) can be performed for histologic diagnosis. In patients with suspected urothelial carcinoma of the prostatic urethra or ducts, resectoscope loop biopsy of the prostatic urethra (at the 5 and 7 o’clock positions from the bladder neck and distally around the area of the verumontanum) can contribute to an improved detection rate [31].

9.5. Radiologic imaging

Radiologic imaging of UC cancer aims to assess local tumour extent and to detect lymphatic and distant metastatic spread. For local staging, increasing evidence indicates that magnetic resonance imaging (MRI) is superior to computed tomography (CT) in terms of staging accuracy. Imaging for regional lymph node metastases should concentrate on
inguinal and pelvic lymph nodes, using either MRI or CT. Distant staging should concentrate on chest and liver, with CT of the thorax and abdomen in all patients with invasive disease (cT1N0M0 [32–36]). If imaging of the remainder of the urothelium is required, CT should include CT urography with an excretory phase [37].

9.6. Regional lymph nodes

In contrast to penile cancer, in which clinically enlarged lymph nodes at initial diagnosis are not uncommon due to inflammatory conditions [38], enlarged lymph nodes in UC often represent metastatic disease [39]. In men, lymphatics from the anterior urethra drain into the superficial and deep inguinal lymph nodes and subsequently to the pelvic (external, obturator, and internal iliac) lymph nodes. Conversely, lymphatic vessels of the posterior urethra drain into the pelvic lymph nodes. In women, the lymph of the proximal third drains into the pelvic lymph node chains, whereas the distal two-thirds initially drains into the superficial and deep inguinal nodes [40,41].

Nodal control in UC can be achieved either by regional lymph node dissection [28], radiotherapy [42], or chemotherapy [39]. Currently, no clear evidence supports prophylactic bilateral inguinal and/or pelvic lymphadenectomy in all patients with UC. However, in patients with clinically enlarged inguinal/pelvic lymph nodes or invasive tumours, regional lymphadenectomy should be considered for initial treatment because cure might still be achievable with limited disease [28].

9.7. Conclusion

Patients with clinically enlarged inguinal or pelvic lymph nodes often exhibit pathologic lymph node metastasis (LE: 3).

9.8. Recommendations

<table>
<thead>
<tr>
<th>Diagnosis includes urethrocystoscopy with biopsy and urinary cytology.</th>
<th>LE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pelvic MRI is the preferred method to assess local extent of urethral tumour.</td>
<td>3</td>
<td>B</td>
</tr>
</tbody>
</table>

10. Treatment of localised primary urethral carcinoma

10.1. Treatment of localised primary urethral carcinoma in men

Treatment of male anterior UC previously followed the procedure for penile cancer, with aggressive surgical excision of the primary lesion with a wide safety margin [28]. Distal urethral tumours exhibit significantly improved survival rates compared with proximal tumours [43]. Therefore, optimising treatment of distal UC has become the focus of clinicians to improve functional outcome and quality of life while preserving oncologic safety. A retrospective series found no evidence of local recurrence, even with <5-mm resection margins (median follow-up: 17–37 mo), in men with pT1–3 N0–2 anterior UC treated with well-defined penis-preserving surgery and additional iliac/inguinal lymphadenectomy for clinically suspected lymph node disease [44]. This suggests that prognosis is mainly determined by nodal stage. Similar results for the feasibility of penile-preserving surgery were reported in other retrospective series [27,45].

10.2. Recommendation

<table>
<thead>
<tr>
<th>In localised anterior urethral tumours, penile-preserving surgery is an alternative to primary urethrectomy if negative surgical margins can be achieved.</th>
<th>LE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT of the thorax and abdomen should be used to assess distant metastases.</td>
<td>3</td>
<td>B</td>
</tr>
</tbody>
</table>

10.3. Treatment of localised urethral carcinoma in females

10.3.1. Urethrectomy and urethra-sparing surgery

In women with localised UC, to provide the highest chance of local cure, primary radical urethrectomy should remove all the periurethral tissue from the bulbocavernosus muscle bilaterally and distally, with a cylinder of all adjacent soft tissue up to the pubic symphysis and bladder neck. Bladder neck closure and proximal diversion through appendicovesicostomy for primary anterior urethral lesions has been shown to provide satisfactory functional results in women [28].

Many recent series have reported outcomes in women with mainly anterior UC undergoing primary treatment with urethra-sparing surgery or radiotherapy, compared with primary urethrectomy, with the aim of maintaining integrity and function of the lower urinary tract [46,47]. In long-term series with a median follow-up of 153–175 mo, local recurrence rates in women undergoing partial urethrectomy with intraoperative frozen section analysis were 22–60%, and distal sleeve resection >2 cm resulted in secondary urinary incontinence in 42% of patients who required additional reconstructive surgery [46,47].

Ablative surgical techniques, that is, transurethral resection (TUR) or laser, used for small distal UC, have also resulted in a considerable local failure rate of 16%, with a cancer-specific survival rate of 50%. This emphasises the critical role of local tumour control in women with distal UC to prevent local and systemic progression [46].

10.3.2. Radiotherapy

In women, radiotherapy was investigated in several older long-term series with a median follow-up of 91–105 mo [42,44]. With a median cumulative dose of 65 Gy (range: 40–106 Gy), the 5-y local control rate was 64%; the 7-y cancer-specific survival was 49% [42]. Most local failures (95%) occurred within the first 2 yr after primary treatment [44]. The extent of urethral tumour involvement...
was found to be the only parameter independently associated with local tumour control, but the type of radiotherapy (external beam vs interstitial brachytherapy) was not [42]. In one study, the addition of brachytherapy to external-beam radiation therapy reduced the risk of local recurrence by a factor of 4.2 [48]. Of note, pelvic toxicity in those achieving local control was considerable (49%) including urethral stenosis, fistula, necrosis, and haemorrhagic cystitis, with 30% of the reported complications graded as severe [42].

10.4. Recommendations

<table>
<thead>
<tr>
<th>LE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>In women with anterior urethral tumours, urethra-sparing surgery is an alternative to primary urethrectomy if negative surgical margins can be achieved intraoperatively.</td>
<td>3</td>
</tr>
<tr>
<td>In women, local radiotherapy is an alternative to urethral surgery for localised urethral tumours.</td>
<td>3</td>
</tr>
</tbody>
</table>

11. Multimodal treatment in advanced urethral carcinoma

11.1. Preoperative cisplatinum-based chemotherapy

Recent retrospective studies have reported that modern cisplatin-based polychemotherapeutic regimens are effective in advanced primary UC, providing prolonged survival even in lymph node–positive disease. They have emphasised the critical role of surgery after chemotherapy for achieving long-term survival in patients with locally advanced UC. The largest retrospective series reported outcomes in 44 patients with advanced primary UC. Patients were subjected to specific cisplatinum-based polychemotherapeutic regimens according to the underlying histology. The overall response rate for the various regimens was 72%. The median overall survival of the entire cohort was 32 mo. Patients who underwent surgery after chemotherapy had significantly improved overall survival compared with those who were managed with chemotherapy alone [39].

11.2. Preoperative chemoradiotherapy in locally advanced squamous cell carcinoma of the urethra

The clinical feasibility of preoperative local radiotherapy with concurrent radiosensitising chemotherapy prior to surgery in locally advanced SCC was reported in several case series [49–53]. The largest and most recent series reported outcomes in 18 patients with primary locally advanced UC. A complete response to primary chemoradiotherapy was observed in 83% of the patients. The 5-yr overall and disease-specific survival was 60% and 83%, respectively. Patients undergoing salvage surgery after chemoradiotherapy experienced a higher 5-yr disease-free survival than those without salvage surgery (72% vs 54%) [54].

11.3. Conclusions

In locally advanced UC, cisplatinum-based chemotherapy with curative intent prior to surgery improves survival compared with surgery alone (LE: 4). In locally advanced SCC of the urethra, the combination of curative radiotherapy with radiosensitising chemotherapy with curative intent prior to surgery improves survival compared with surgery alone (LE: 4).

11.4. Recommendations

<table>
<thead>
<tr>
<th>LE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with locally advanced UC should be discussed by a multidisciplinary team of urologists, radiation oncologists, and oncologists.</td>
<td>4</td>
</tr>
<tr>
<td>Chemotherapeutic regimens with curative intent should be cisplatinum based.</td>
<td>4</td>
</tr>
<tr>
<td>In locally advanced SCC of the urethra, chemoradiotherapy with curative intent prior to surgery is an option.</td>
<td>4</td>
</tr>
</tbody>
</table>

12. Treatment of urothelial carcinoma of the prostate

Local conservative treatment with extensive TUR and subsequent bacillus Calmette-Guérin (BCG) instillation is effective in patients with Ta or Tis prostatic UC [55,56]. Patients undergoing TUR of the prostate prior to BCG experience improved complete response rates compared with those who do not (95% vs 66%) [57]. The risk of understaging local extension of prostatic UC at TUR is increased, especially in patients with ductal or stromal involvement [58]. In smaller series, response rates to BCG in patients with prostatic duct involvement were reported to vary between 57% and 75% [55,59]. Some former series have reported superior oncologic results for the initial use of radical cystoprostatectomy as a primary treatment option in patients with ductal involvement [60,61]. In 24 patients with prostatic stromal invasion treated with radical cystoprostatectomy, a lymph node mapping study found that 12 patients had positive lymph nodes, with an increased proportion located above the iliac bifurcation [62].

12.1. Recommendations

<table>
<thead>
<tr>
<th>LE</th>
<th>GR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with noninvasive UC or carcinoma in situ of the prostatic urethra and prostatic ducts can be treated with a urethra-sparing approach with TUR and BCG.</td>
<td>3</td>
</tr>
<tr>
<td>In patients with noninvasive UC or carcinoma in situ, prior TUR of the prostate should be performed to improve response to BCG.</td>
<td>3</td>
</tr>
<tr>
<td>Cystoprostatectomy with extended pelvic lymphadenectomy should be reserved for patients not responding to BCG or a primary treatment option in patients with extensive ductal or stromal involvement.</td>
<td>3</td>
</tr>
</tbody>
</table>
Cystoprostatectomy with extended pelvic lymphadenectomy should be reserved for patients not responding to BCG or as a primary treatment option in patients with extensive ductal or stromal involvement (LE: 3; GR: C).

13. Follow-up

Given the low incidence of primary UC, defined follow-up has not been investigated systematically so far. Therefore, it seems prudent to advocate a more extensive follow-up with urinary cytology, urethrocytoscoppy, and cross-sectional imaging despite the lack of specific data.

Author contributions: Georgios Gakis had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Gakis.

Acquisition of data: Gakis.

Analysis and interpretation of data: Gakis, Witjes, Cowan, Ribale, Lebret, De Santis, Sherif, Compe´rat.

Drafting of the manuscript: Gakis.

Critical revision of the manuscript for important intellectual content: Gakis, Witjes, Cowan, Ribale, Lebret, De Santis, Sherif, Compe´rat.

Statistical analysis: Gakis.

Obtaining funding: None.

Administrative, technical, or material support: Gakis.

Supervision: Gakis, Witjes.

Other (specify): None.

Financial disclosures: Georgios Gakis certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: J. Alfred Witjes is a company consultant for Endo Pharm, Astellas, Ipsen and Allergan, Sanofi Pasteur, GE Healthcare, and Telormedix. He receives company speaker honoraria from GE Healthcare, MEL Amsterdam, Photocure, and Ipsen. He participates in trials for MEL Amsterdam, Telormedix, and Photocure Oslo. Maria De Santis is a company consultant for Glaxo Smith Kline, AMGEN, Bayer, Novartis, Pierre-Fabre, Roche, Dendreon, Teva, Pfizer, and Janssen. She receives company speaker honoraria from Eli Lilly, Sanofi Aventis, Novartis, Roche, and Janssen. She participates in trials for Pierre-Fabre, Millennium, and Dendreon. She receives fellowships and travel grants from Bayer, Novartis, Pfizer, AMGEN, Sanofi Aventis, and Roche, and research grants from Pierre Fabre. Amir M. Sherif receives company speaker honoraria from Orion Pharma and MEDAC AB. Thierry Lebret is a company consultant for Ipsen, Novartis, Amgen, and Sanofi. He receives company honoraria from Ferring and participates in trials for Astellas and Takeda. Maria J. Ribal is an advisory board member at Jansen Pharmaceuticals. She receives company speaker honoraria from Jansen Pharmaceuticals, Olympus, and Ipsen. The remaining authors have nothing to disclose.

Funding/Support and role of the sponsor: None.

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