Staging practice for prostate cancer varies and is not in line with clinical guidelines

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ABSTRACT

INTRODUCTION: The objective was to describe regional variations in M-staging in patients with newly diagnosed prostate cancer within a Danish county and to compare clinical practice with guideline recommendations.

METHODS: Data were as captured from 1) a prospective, non-interventional study counting 635 consecutive patients referred for M-staging in the 2008-2009 period at three regional hospitals within one county, and 2) a questionnaire on M-staging practice completed by the five sites performing M-staging in the same county in 2015.

RESULTS: All three sites referred patients for M-staging in 2008, irrespective of their risk factors. Two of the three sites maintained this practice in 2015. Furthermore, in 2015, three of five sites performed M-staging in intermediate and high-risk patients only. Planar whole-body bone scans were standard in all sites in 2008 with single photon emission/computed tomography (SPECT/CT) being performed if required and if available. In 2015, two sites used choline positron emission tomography/CT for primary staging of high-risk patients against guideline recommendations. The use of SPECT/CT showed wide variations from "if required" to "ma ndatory" head-to-thigh imaging. There were notable variations between clinical practice and guidelines in 2008, and this was even more evident in 2015.

CONCLUSION: Considerable variations existed with respect to the M-staging imaging practices in prostate cancer within a single Danish county. The variation was more pronounced in 2015 than in 2008. Clinical practice conflicted in part with European and national Danish guidelines.

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Bone imaging is the cornerstone in the staging of prostate cancer patients. A number of trials indicate that patients with a low risk do not require M-staging [1]. The risk classification is based on prostate-specific antigen (PSA) levels, T-stage and Gleason grade [2]. International clinical guidelines, including the European Association of Urology (EAU) [2] and the National Comprehensive Cancer Center (NCCN) [3] as well as Danish guidelines [4, 5], have provided recommendations describing which patients should be scanned. Despite knowledge of the lack of compliance with guidelines in clinical practice in general [6, 7], no quality measures are in place to ensure high-quality medical practice in this area. Even though there are some discrepancies in guidelines describing which patients to scan [8, 9], the guidelines have been quite uniform for many years in their recommendations of bone scintigraphy (BS) as the preferred imaging technique. The recommendations of planar whole-body bone scintigraphy (WB-BS) (**Figure 1**) continue to be in force despite a number of reports showing promising diagnostic properties of novel methods such as magnetic resonance imaging (MRI), single-photon emission computed tomography (SPECT)/CT and positron emission tomography (PET)/CT with ^{11}C- or ^{18}F-choline or ^{18}F-sodium fluoride. However, the recommendation to use WB-BS is likely owed to its acceptable sensitivity, wide availability and low cost.

We recently presented data from a large prospective study on the diagnostic value of BS in the initial staging of prostate cancer [10]. The review of these data from 2008-2009 indicated wide variations in M-staging practices among the recruiting sites. The purpose of the present paper was to describe the variation in M-staging practices within a single Danish county and to assess if practices had changed by 2015. The clinical practice was compared with European and Danish guidelines.

METHODS

M-staging practices in 2008-2009

A total of 635 consecutive patients were enrolled in a study performed 2008-2009 in three sites in the Central Denmark Region [10]. This non-interventional, prospective study was performed as part of normal clinical practice. BS reports were approved by a minimum of one nuclear medicine specialist at all sites. The clinical data were retrieved from hospital records. The study sites were anonymised to avoid exposure of individual departments. The study was approved by the Danish Data Protection Agency. The Danish Health Authority provided a waiver for informed consent to medical files.

The procedure for M-staging was registered, including the use of SPECT/CT and additional radiological imaging with MRI and/or CT. At one site, CT was used for nodal staging in patients scheduled for curative treatment; here the pelvic images were reviewed in "bone window" for the assessment of bone metastasis. CT and MRI were available at all sites.

ORIGINAL ARTICLE

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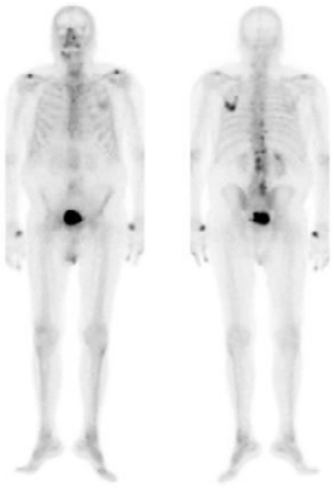
FIGURE 1

Bone scintigraphy (anterior view, left; posterior view, right) of a prostate cancer patient with bone metastasis.



M-staging practice in 2015

Information about the 2015 procedures for M-staging at the three sites was collected by telephone calls and e-mail correspondence towards the end of 2015. We called the physicians in charge of prostate cancer at each site, specifically at the departments of urology and nuclear medicine. Due to administrative changes, one site (Site 1) was no longer an individual hospital unit; rather it was served by the university hospital in the region (Aarhus University Hospital). In addition, the university hospital provided clinical services for another regional hospital, which we also included in the 2015 survey in order to cover the diagnostic pattern in the entire county. Thus, the M-staging practices in five sites in the county were investigated. The five sites referred patients to four nuclear medicine departments.

Trial registration: not relevant (as this was a non-intervention study).

RESULTS

Selection of patients for M-staging

In 2008-2009, the sites performed M-staging in all patients, irrespective of their risk classification (**Table 1**). One site (Site 2) had institutional instructions in place only to perform staging in patients with a PSA concentration > 10 ng/ml or Gleason score > 7. However, 54 of 225 (24.0%) patients from Site 2 did have PSA and Gleason values below the institutional requirements for M-staging. Thus, in general, all patients were referred for M-staging in 2008-2009. In 2015, two sites (Sites 1 and 2) continued to perform M-staging in the same way they had done in 2008-2009 (Table 1). The university clinic took over the clinical responsibilities previously provided by Site 3 and introduced the D'Amico criteria for M-staging here as well as for another regional clinic (Site 4) and the university hospital itself (Site 5). Some variation was observed with respect to D'Amico and the EAU risk classifications over time, but these variations are identical in the 2015 EAU guidance (low risk: T1-2a, PSA concentration < 10 ng/ml, Gleason score < 7; intermediary; T2b, Gleason score 7 or PSA concentration 10-20 ng/ml, and high; T2c-3, Gleason score > 7, PSA concentration > 20 ng/ml).

Imaging modalities used for M-staging

In 2008, all sites used nuclear medicine technologies as the primary method for M-staging (**Table 2**). In the case of an equivocal WB-BS, SPECT/CT, acquisition of the BS as well as additional CT or MRI imaging could be performed. The decision to do a SPECT/CT was taken by a nuclear medicine physician immediately after acquisition of the WB-BS, whereas the urologists referred patients for CT or MRI. All SPECT/CT investigations were performed "if required", i.e. based on equivocal WB-BS results. The use of CT for additional imaging was generally low. However, one site (Site 1) used CT for nodal staging, and this site used CT images in "bone window mode" to assess skeletal malignancy. Furthermore, Site 1 used MR in only 12% of the cases with equivocal WB-BS results compared with 73-97% at the two other sites.

The M-staging procedure changed notably from 2008 to 2015. Whereas WB-BS was the preferred method in all sites in 2008, patients with D'Amico high-risk disease were referred from several sites to ^{18}F-choline PET/CT as the primary imaging method in 2015 (Table 2). In the remaining sites, WB-BS remained the preferred scanning technique. The use of additional SPECT/CT varied across sites. Some sites only used SPECT/CT if the initial WB-BS showed suspicious lesions, whereas one site acquired SPECT/CT of the pelvis irre-

TABLE 1

Patient criteria for M-staging in 2008-2009 versus 2015.

Site	2008-2009	2015
1	All patients	All patients
2	PSA concentration > 10 ng/ml or Gleason score > 7	PSA concentration > 10 ng/ml or Gleason score > 7
3	All patients	D'Amico criteria intermediate and high risk
4	NA	D'Amico criteria intermediate and high risk
5	NA	D'Amico criteria intermediate and high risk

NA = not available; PSA = prostate-specific antigen.

spective of the WB-BS findings. Patients from two sites had WB-BS plus mandatory SPECT/CT from the head to the upper thigh. All sites stated that MRI was their preferred additional imaging modality (some sites preferred CT for ribs) in case of unclear or equivocal BS or PET results.

Compliance with guidelines

The results were compared with the recommendations in the clinical guidelines issued by Danish and European (EAU) urological organisations (**Table 3**). The current Danish guideline in 2008-2009 was the 2005 Danish Prostate Cancer Guideline [4]. The EAU guideline from 2008 [11] and 2015 (Mottet et al, available from EAU home page) were used for comparison. The Danish 2015 guideline on imaging in prostate cancer was issued by The Danish Prostate Cancer Group [5]. The main differences between guidelines (Table 3) and clinical practice (Table 1 and Table 2) in 2008-2009 were the selection of patients for M-staging and the use of supplementary SPECT/CT. The main differences in 2015 were the use of PET/CT for primary staging, and the extensive use of SPECT/CT.

DISCUSSION

This study compared M-staging practise in prostate cancer within a single Danish county in the 2008-2015 period. Data in 2008 showed large differences regarding which patients to scan and how to perform the M-staging. The criteria for performing M-staging showed even larger variations in 2015. Interestingly, lack of compliance with both national and international guidelines was present at both time points. Whereas overuse of M-staging based on risk factors was evident in 2008, data from 2015 showed use of imaging methods that were either not recommended or which should be avoided according to international guidelines.

An increasing amount of data indicates that M-staging can be omitted in patients with a low risk. Both Danish and European guidelines provided recommendations in 2008-2009 about which patients not to scan [4, 11]. However, none of three sites complied fully with these recommendations. In 2015, most sites complied with the 2015 guideline recommendations, but some departments maintained their 2008 practice to scan all or the majority of patients. The over-use of M-staging in prostate cancer with costly PET/CT has been much debated in the US [12]. It is certainly possible to reduce in-

TABLE 2

The primary imaging methods and use of SPECT/CT in 2008 versus 2015.

	Primary M-staging method		SPECT/CT	
Site	2008	2015	2008	2015
1	WB-BS	WB-BS	If required[a]	If required
2	WB-BS	WB-BS	NA	If required
3	WB-BS	WB-BS	If required[b]	Pelvis mandatory
4	NA	WB-BS: D'Amico criterion intermediate risk ^{18}F-choline PET/CT: D'Amico criterion high risk	NA	Head-to-thigh mandatory None
5	NA	WB-BS: D'Amico criterion intermediate risk ^{18}F-choline PET/CT: D'Amico criterion high risk	NA	Head-to-thigh mandatory None

NA = not available; SPECT/CT = single photon emission computed tomography/computed tomography; WB-BS = whole-body bone scintigraphy.
a) Available for the entire study; b) Introduced halfway through the recruitment period.

TABLE 3

Recommendations for M-staging in Danish and European Association of Urology guidelines 2008 and 2015.

	2008		2015	
Items	Denmark	EAU	Denmark	EAU
Criteria for avoiding M-staging: do not do if	Asymptomatic *and* PSA concentration < 20 ng/ml *and* Gleason score ≤ 6 If planned curative treatment: asymptomatic *and* PSA concentration < 10 ng/ml *and* Gleason score ≤ 6	Asymptomatic *and* PSA concentration < 20 ng/ml *and* well- or moderately differentiated tumours	Asymptomatic low EAU risk patients: PSA concentration < 10 ng/ml *and* Gleason score < 7 *and* cT1-2a Asymptomatic intermediate EAU risk patients: PSA concentration 10-20 ng/ml *and* Gleason score 7 *and* cT2b, if preferable Gleason score 4 pattern "4 + 3"	Asymptomatic low EAU risk patients: PSA concentration < 10 ng/ml *and* Gleason score < 7 *and* cT1-2a Asymptomatic intermediate EAU risk patients: PSA concentration 10-20 ng/ml *and* Gleason score 7 *and* cT2b, if preferable Gleason score 4 pattern "4 + 3"
Primary method recommended for M-staging	BS	BS	BS	BS
Advise of primary use of PET/CT	Not mentioned	Not mentioned	Not mentioned	Should not be used
Supplementary SPECT/CT	Not mentioned	Not mentioned	Add-on if equivocal BS findings	Not mentioned
Additional imaging: MRI/CT	Not mentioned	Not mentioned	MRI or CT	Other imaging modalities: not specified

BS = bone scintigraphy; CT = computed tomography; EAU = European Association of Urology; MRI = magnetic resonance imaging; PSA = prostate-specific antigen; SPECT = single photon emission computed tomography.

appropriate BS as shown in Sweden by Malkarov et al, particularly in low-risk patients [13]. Via a campaign introduced in 2000, inappropriate BS was reduced from 45% in 1998 to 3% in 2009.

All sites used nuclear medicine methods for M-staging in 2008 and also in 2015. These procedures are in line with Danish and European recommendations. During the past decade, PET/CT has reshaped nuclear medicine owing to technical improvements in image quality and to the development of attractive ligands for prostate cancer, e.g. ^{11}C- or ^{18}F-choline and ^{18}F-sodium fluoride. Although several systematic reviews shows that choline PET outperforms WB-BS for detection of bone metastasis, the vast majority of data are based on recurrent disease, not staging. Thus, key international guidelines recommend against the use of PET for M-staging [2, 3]. It is remarkable that Danish sites perform procedures that are squarely against Danish and European guidelines.

A notable proportion of WB-BS turned out to be equivocal for bone metastasis. SPECT/CT is a hybrid imaging technique which combines BS acquired with a tomographic gamma camera with low-dose CT. This allows for three-dimensional reconstruction and exact anatomical localisation of hot spots seen on WB-BS, which yield a superior diagnostic performance compared with WB-BS [14]. Still, apart from the NCCN guidelines, all clinical guidelines in prostate cancer fail to mention SPECT/CT. The clinical position of SPECT/CT is probably not clear due to the heterogeneous use reported.

In the case of unclear nuclear medicine investigation, MR was consistently shown to be the preferred method for additional imaging. In the 2008 trial, one site did CT for nodal staging and used that CT in most patients with equivocal bone scans. In 2015, all sites recommended MRI.

The study revealed a varying degree of compliance with Danish and European guidelines. However, we also noted some differences in recommendations across guidelines. These inconsistencies among guidelines have been shown in different aspects of management of prostate cancer [9, 15]. For example, the clinical criteria for M-staging in newly diagnosed prostate cancer are not consistent between guidelines [8, 9]. Part of the discrepancy may be due to guideline development [16]. The apparent discrepancy between local and European prostate cancer guidelines has recently been discussed in Norway [17]. In 2015, there appeared to be only minor differences between Danish and European guidelines for M-staging.

It remains only partly explained why physicians do not follow guidelines, in particular national guidelines. The time lag for implementation of new practises and/or the only partial acceptance in the clinic of the guidelines have been identified as main barriers for compliance [18]. A recent systematic review highlighted activities that could improve the implementation of guidelines [7]. A multidisciplinary approach may improve guideline implementation [6]. The inclusion of imaging practice in patient-reported outcome measures (e.g. the Danish prostate cancer register, DaProCaData) will likely improve the documentation of practice and highlight regional differences. Such registration may also report over-usage of investigations [12]. All attempts to improve compliance with guidelines are encouraged since compliance with guidelines can improve patient outcome, including survival [19, 20].

CONCLUSION

We conclude that referral patterns and procedures for M-staging varied notable within a single Danish county. Some non-compliance with Danish and European guidelines was reported. For various reasons, including the cost and quality of patient care, adherence to evidence-based guidelines should be emphasised.

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LITERATURE

1. Biganti A, Suardi N, Gallina A et al. Predicting the risk of bone metastasis in prostate cancer. Cancer Treat Rev 2014;40:3-11.
2. Heidenreich A, Bastian PJ, Bellmunt J et al. EAU guidelines on prostate cancer. part 1: screening, diagnosis, and local treatment with curative intent-update 2013. Eur Urol 2014;65:124-37.
3. Mohler JL, Kantoff PW, Armstrong AJ et al. Prostate cancer, version 2. 2014. J Natl Compr Canc Netw 2014;12:686-718.
4. Mommsen SB, K. Graversen P, Iversen P et al. Prostatabetænkning 2005. Copenhagen. 2005.
5. Petersen LJ, Pedersen BG. Billeddiagnostik. In: DUCG´s Nationale Retningslinier for Diagnostik og Behandling af Prostata Cancer. Danish Urological Cancer Group, 2016: Kap. 23. http://ducg.dk/fileadmin/www.ducg.dk/Prostatacancer/Kl._retningslinjer/2015/23._Billeddiagnostik_10_JUL_2015.pdf (1 Jun 2016).
6. Mahe I, Chidiac J, Helfer H et al. Factors influencing adherence to clinical guidelines in the management of cancer associated thrombosis. J Thromb Haemost 2016 (e-pub ahead of print).
7. Flodgren G, Hall AM, Goulding L et al. Tools developed and disseminated by guideline producers to promote the uptake of their guidelines. Cochrane Database Syst Rev 2016;8:CD010669.
8. Zacho HD, Barsi T, Mortensen JC et al. Validation of contemporary guidelines for bone scintigraphy in prostate cancer staging: a prospective study in patients undergoing radical prostatectomy. Scand J Urol 2016; 50:29-32.
9. Crawford ED, Stone NN, Yu EY et al. Challenges and recommendations for early identification of metastatic disease in prostate cancer. Urology 2014;83:664-9.
10. Zacho HD, Barsi T, Mortensen JC et al. Prospective multicenter study of bone scintigraphy in consecutive patients with newly diagnosed prostate cancer. Clin Nucl Med 2014;39:26-31.
11. Heidenreich A, Aus G, Bolla M et al. EAU guidelines on prostate cancer. Eur Urol 2008;53:68-80.
12. Schnipper LE, Smith TJ, Raghavan D et al. American Society of Clinical Oncology identifies five key opportunities to improve care and reduce costs: the top five list for oncology. J Clin Oncol 2012;30:1715-24.
13. Makarov DV, Loeb S, Ulmert D et al. Prostate cancer imaging trends after a nationwide effort to discourage inappropriate prostate cancer imaging. J Natl Cancer Inst 2013;105:1306-13.
14. Palmedo H, Marx C, Ebert A et al. Whole-body SPECT/CT for bone scintigraphy: diagnostic value and effect on patient management in oncological patients. Eur J Nucl Med Mol Imaging 2014;41:59-67.
15. Vickers AJ, Till C, Tangen CM et al. An empirical evaluation of guidelines on prostate-specific antigen velocity in prostate cancer detection. J Natl Cancer Inst 2011;103:462-9.
16. Cahalane AM, Purcell YM, Lavelle LP et al. Which is the best current

guideline for the diagnosis and management of cystic pancreatic neoplasms? An appraisal using evidence-based practice methods. Eur Radiol 2016;26:3121-8.
17. Johansen TE. [Different guidelines for treatment of prostate cancer]. Tidsskr Nor Laegeforen 2015;135:924-5.
18. Carthey J, Walker S, Deelchand V et al. Breaking the rules: understanding non-compliance with policies and guidelines. BMJ 2011;343:d5283.
19. Molena D, Mungo B, Stem M et al. Does quality of care matter? A study of adherence to National Comprehensive Cancer Network Guidelines for patients with locally advanced esophageal cancer. J Gastrointest Surg 2015;19:1739-47.
20. Falstie-Jensen AM, Larsson H, Hollnagel E et al. Compliance with hospital accreditation and patient mortality: a Danish nationwide population-based study. Int J Qual Health Care 2015;27:165-74.