Cervical cancer staging, pretreatment planning and surgical treatment in the Nordic countries – survey from the Surgical Subcommittee of the Nordic Society of Gynecological Oncology

Running headline: Cervical cancer in the Nordic countries

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Conflicts of Interest notification
The authors have stated explicitly that there are no conflicts of interest in connection with this article.

Abstract
Introduction: Cervical cancer patients in the Nordic countries are increasingly undergoing pretreatment imaging by ultrasound, magnetic resonance imaging (MRI), position emission tomography – computed tomography (PET-CT) or computed tomography, or sentinel lymph node (SLN) procedure. The present survey reports the influence of pretreatment imaging findings on the recorded clinical International Federation of Gynecology and Obstetrics (FIGO) stage in Nordic countries and its impact on treatment planning and preferred surgical approach in cervical cancer.

Material and methods: The Nordic Society of Gynecologic Oncology (NSGO) Surgical Subcommittee developed a questionnaire-based survey that was conducted from 1 January to 31 March 2017. All the 22 Nordic Gynecological Oncology Centers (Denmark 5, Finland 5, Iceland 1, Norway 4, and Sweden 7) were invited to participate.

Results: The questionnaires were returned by 19 of 22 (86.3%) centers. The median number (range) of cervical cancer patients treated at each center annually was 32 (15-120). In 58% (11/19) of the centers, imaging findings were reported to influence the clinical staging. MRI in combination with PET-CT was the preferred imaging methods and the results influenced treatment planning. Robotic-assisted radical hysterectomy was the preferred surgical method in 72% (13/18) of the centers. Sentinel lymph node procedure was not routinely implemented in the majority of the Nordic centers.
Conclusion: More than half of the Nordic Gynecological Oncology Centers already report a clinical FIGO stage influenced by pretreatment imaging findings. The trend in preferred treatment is robotic-assisted radical hysterectomy and the sentinel lymph node procedure is gradually introduced.

Keywords
Uterine Cervical Neoplasm; Neoplasm Staging; pretreatment elaboration; Diagnostic Imaging; Gynecologic Surgical Procedure; Sentinel Lymph Node; FIGO; NSGO.

Abbreviations
ESGO-ESMO-ESP European Society of Gynecological Oncology – European Society for Medical Oncology – European Society of Pathology;
FIGO International Federation of Gynecology and Obstetrics;
MRI magnetic resonance imaging;
NSGO Nordic Society of Gynecological Oncology;
PET-CT positron emission tomography-computed tomography;
SLN sentinel lymph node;
TNM Tumor, Node and Metastasis;

Key Message
In cervical cancer coherence to FIGO clinical staging is challenged in the Nordic countries. Pretreatment diagnostic imaging is reported to affect the FIGO stage in more than half of the centers. The preferred surgical treatment is robotic-assisted radical hysterectomy.

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Introduction

For cervical cancer, clinical staging is most often used in accordance with the International Federation of Gynecology and Obstetrics (FIGO) staging system. The staging system is based on the results of physical examination and biopsies (1). Although recommended, imaging is not mandatory and findings at surgery should not change the clinical stage. Furthermore, FIGO staging system for cervical cancer does not take lymph node metastases into account. It is unknown to what extent results from imaging examinations influence clinical staging of cervical cancer.

Cervical cancer staging is the oldest staging system in the literature, dating back in 1928, when a sub-commission of the League of Nations formulated staging rules to facilitate comparison of treatment results (2). Based on findings at physical examination under anesthesia before treatment, the extent of disease was clinically staged into one of four stages, and the results were recorded in a uniform way. Cases were reported in the Annual Report under the patronage of the League of Nations. In 1958, the responsibility was taken over by FIGO. The Annual Report was substituted by the FIGO Cancer Report launched in 2012, the latest issued 2015 (3,4). This report includes updates on staging and management guidelines on site-specific gynecological cancer.

A second staging system, the Tumor, Node and Metastasis (TNM) classification, was adopted by the International Union Against Cancer (UICC) in 1966 and the American Joint Commission on Cancer (AJCC) in 1976 (5). Although the TNM classification has been widely adopted for staging most cancers, the FIGO classification is still the most commonly used staging system for female genital cancers. Several modifications to the FIGO classification and staging of cervical cancer has been adopted, and the rational for keeping clinical staging instead of surgical staging is described in detail by Pecorelli(1). The rationale for the clinical approach is that 85-90% of all new cervical cancer cases are diagnosed in low-income regions(3,4,6), where both screening and vaccination is sparse(7). Therefore, the majority of women with cervical cancer will be staged according to the FIGO guideline and thereby ensure globally comparability of outcomes.

According to the latest FIGO staging guidelines, examination under anesthesia, cystoscopy, sigmoidoscopy and intravenous pyelography are no longer mandatory and radiological tumor volume as well as parametrial invasion should be recorded separately.
In the Nordic countries, the annual incidence of new cervical cancer cases was 1390 in 2011-2015 (8). Pretreatment planning at multidisciplinary team meetings incorporating findings from imaging examinations such as ultrasound, magnetic resonance imaging (MRI), position emission tomography – computed tomography (PET-CT) or computed tomography and sentinel lymph node (SLN) procedure, is currently part of the routine patient care in cervical cancer patients in many Nordic centers.

Following discussions within the Surgical Subcommittee of the Nordic Society of Gynecologic Oncology (NSGO), the aim of the present study was to explore the routine diagnostic work-up and role of pretreatment diagnostic imaging on clinical staging, pretreatment planning and preferred surgical approach in cervical cancer at the Gynecological Oncology Centers in the Nordic countries.

Material and Methods

A 15-question electronic survey was distributed, between 1 January to 31 March 2017, to the lead physician at the 22 University Hospitals in Nordic countries harboring a Gynecological Oncology Center (five in Denmark, five in Finland, one in Iceland, four in Norway, and seven in Sweden) (Supporting Information Appendix S1). In Sweden, gynecologic oncology is a non-surgical specialty; hence cervical cancer surgery is performed in six of the seven University Hospitals.

Question 1 and 2 were demographic questions. Questions 3 and 4 surveyed the number of incident cervical cancer cases treated annually and the number of surgeons performing radical hysterectomy. Questions 5 through 9 assessed the type of imaging used for diagnostic work-up, when the imaging results are disclosed in relation to multidisciplinary team meetings and to the allocation of FIGO stage, if the results from the diagnostic imaging influence the final clinical staging and treatment provided. Questions 10-12 covered questions of surgical techniques for cervical cancer, histologic verification of suspicious lymph node metastases and further management in case of peroperative finding of lymph node metastases. Question 13 covered database registration of imaging findings. Questions 14 and 15 surveyed the use of the SLN procedure in cervical cancer including the type of technique.
Results

Physicians from a total of 19 of 22 (86%) Nordic Gynecological Oncology Centers completed the survey. The response rate was 100% in Denmark, Finland and Iceland, 86% (6 of 7) in Sweden and 50% (2 of 4) in Norway. The median (range) number of new cervical cancer cases treated annually at each center was 32 (15-120). Two to five surgeons performed the radical hysterectomy in each institution.

Table 1 shows the number and type of routinely employed imaging modalities in the diagnostic work-up of newly diagnosed cervical cancer at the Nordic Gynecological Oncology Centers. All centers used imaging at the diagnostic work-up. MRI was performed in 18 (95%) centers and combined with at least one other imaging modality, most commonly with PET-CT (83%). In one center, PET-CT was used alone. Physical examination was reported to be the sole method to assess parametrial tumor infiltration by six of 19 (32%) centers. For tumor size assessments, three of 19 (16%) centers used clinical examination only, whereas three of 19 (16%) centers based this solely on MRI evaluations. The remaining 13 of 19 (68%) centers reported that tumor size assessment was estimated by a combination of clinical and imaging examinations. All, but one center, reported evaluation of imaging at multidisciplinary team meetings. Evaluation of imaging results before clinical staging was reported to be routinely performed in 78% (14 of 18), and after clinical staging in 17% (3 of 18) of the institutions. In total, 11 of 19 (58%) Nordic Gynecological Oncology Centers reported that results from diagnostic imaging had an impact on the recorded clinical FIGO stage.

In 17 of 19 (89%) centers, imaging findings were reported to definitely influence the treatment planning, and in the remaining two centers the imaging findings were reported to possibly influence the choice of treatment.

The surgical procedures were reported by 18 centers (Table 1). Robotic-assisted radical hysterectomy was performed in all centers. In 72% (13 of 18) this was reported as the preferred method, and the remaining centers reported to perform a combination of robotic-assisted, laparoscopic and abdominal radical hysterectomy. In three (17%) centers SLN procedure was reported as established practice, in five (28%) only as part of a protocol and in one center (6%) the SLN procedure was reported to be
performed as established practice as well as part of protocolled trials. Half of the centers reportedly did not perform the SLN procedure.

In 10 of 14 centers, not performing routinely SLN procedure, a radiologically detected suspicious lymph node would call for histologic or cytologic verification of metastatic spread. The method of choice was reported to be laparoscopic biopsy in seven of 14 centers (50%) and fine needle aspiration in three of 14 (21%) centers. Hence no histologic or cytologic verification was obtained in four (29%) centers. If lymph node metastases, confirmed by either frozen section or bulky nodes, were detected during surgery, 13 of 14 centers reported that surgery would be discontinued and the patient referred for chemo-radiation. One center preferred to complete surgery and thereafter refer the patient for chemo-radiation.

Discussion

The majority of Nordic Gynecologic Oncology Centers reported that the results from diagnostic imaging had an impact on the recorded clinical FIGO stage. Physical examination was the sole method to estimate parametrial tumor infiltration in one third of the centers and to estimate tumor size in one out of six centers. MRI in combination with PET-CT was the preferred imaging methods and the imaging results influenced treatment planning. Robotic-assisted radical hysterectomy was reported to be standard surgical treatment but the SLN procedure was not routinely implemented in the majority of Nordic centers.

We are not aware of other surveys to report the influence of the clinical practice leading to a discrepancy in the clinical FIGO stage and the actual reported FIGO stage. In the present study, more than half of the Nordic Gynecologic Oncology Centers report that the clinical FIGO stage is influenced by pretreatment imaging findings. The impact of the physical examination is declining as only on third of the centers rely on these findings alone. As a consequence, the use of imaging methods in the treatment planning may have an impact on and bias the survival data based earlier entirely on clinical FIGO stage. This may especially apply to low-income countries and high-income countries having very different access to imaging facilities at diagnostic work-up.
The introduction of imaging in treatment planning enables a more meticulous and individualized treatment planning (9-11). It facilitates a reduction in the number of women treated both with surgical treatment and chemo-radiation and in addition induces a safer adaption of the treatment to the patient’s preference, often dependent on the age and future fertility desire. In the Nordic Gynecological Oncology Centers, there is a reported tendency towards relying on imaging. This is becoming increasingly important in treatment planning and the present survey highlights the frequent use of MRI for tumor size assessment and parametrial invasion and PET-CT for the evaluation of lymph node involvement, though the use of imaging methods is not uniform across the centers. The diversity of approaches at different centers may also reflect the ever-evolving amendments of clinical guidelines that are gradually adapted into the clinical practice as well as local traditions regarding cervical cancer patient care.

The treatment recommendations for cervical cancer in the FIGO report 2012(3) is schematized in Table 2 with amendments in the FIGO report 2015(4) and from the recently released European Society of Gynaecological Oncology – European Society for Medical Oncology – European Society of Pathology (ESGO-ESMO-ESP) Guideline for Management of Patients with Cervical Cancer (12). The latter recommend FIGO staging plus staging according to the TNM classification and that the TNM classification is based on results from clinical examination, imaging, and/or pathology. The major change in the recommendations after 2012 is an increased focus on tumor size, dividing at 2 and 4 cm. Thereby, striving towards less radical surgery in the earliest stages with tumor < 2 cm, and augment fertility sparing opportunities in younger women and inducing less morbidity after treatment. In tumors between 2 and 4 cm, the main goal is to avoid both radical surgery and chemo-radiation. For stage 1B2 to 2A, the outcome is comparable when treatment is given as either surgery or chemo-radiation, but when given in combination the side effects are intensified(13,14). The tumor size have an increased importance in the treatment planning, therefore pretreatment MRI (see Figure 1) to support the physical assessment of tumor size and parametrial invasion in the treatment planning has become common practice. More than half of the Nordic Gynecological Oncology Centers reported a derivative effect on the reported clinical FIGO stage.

Pretreatment assessment of lymph node status by PET-CT (Figure 1) was reportedly performed in the majority of the Nordic Gynecological Oncology Centers. The presence of lymph node metastases is important for the treatment planning. Verification of suspicious lymph nodes by PET-CT helps to reduce the number of women given both radical surgery and adjuvant chemo-radiation, thereby leading to a reduction in the experienced adverse events (4,15,16). The risk for pelvic lymph node metastases is not significant in stage 1A1, in stage 1A2 there is a small potential risk, in stage 1B1 the
risk is 16% and in 1B2 36%(3). In tumors above 4 cm, the presence of para-aortic lymph node metastases is important for treatment planning. The reported risk of para-aortic lymph nodes is for stage 2B; 21%-35%, stage 3; 20-31% and stage 4; 13%(17,18). At the Nordic centers, the verification of suspicious lymph nodes by PET-CT influenced the treatment planning in different ways, for example initiation of primary chemo-radiation without further elaboration to cytologic verification by fine needle aspiration, histologic verification after laparoscopic biopsy or SLN procedure prior to further treatment decision. Referring to the guidelines (Table 2), there is a tendency towards per-operative verification of lymph node metastases either by pelvic lymph node excision or SLN procedure. The present survey reports a wide variation in the approach to suspicious pelvic lymph nodes comparable with the on-going amendments and discussions of both the guidelines in cervical cancer.

Robotic assisted radical hysterectomy is reported to be the preferred standard surgical method in the Nordic Gynecological Oncology Centers; nevertheless SLN procedure is reportedly only standard procedure in four centers. It appears that the aim of almost all centers is to prevent treatment with the combination of radical surgery and chemo-radiation, since only one center reports that they normally complete radical surgery even when suspicious lymph nodes are detected during surgery. Especially, the SLN procedure has been discussed since the 1990’s, and by Salvo et al. recently suggested the SLN procedure as the standard of care for women with early-stage cervical cancer(19). Nevertheless, no randomized controlled studies have been performed, and therefore the SLN procedure is still only a suggested possibility, even in the latest guideline from ESGO-ESMO-ESP from 2017(12).

In conclusion, the present study from the Nordic Gynecological Oncology Centers documents an increased use of diagnostic imaging in the pretreatment work-up, which in more than half of the centers is reported to influence on the reported clinical FIGO stage. The Surgical Subcommittee of the NSGO respects FIGO’s aim of global comparability and welcomes the initiative from ESGO-ESMO-ESP 2017 promoting the implementation of a clinical, imaging and pathological TNM stage(12). With this survey, we would like to encourage that in the future, FIGO staging of cervical cancer will be either surgically staged like all other cancers of the genital tract(1) or clinical, imaging and/or surgical, dependent on the resources available. The NSGO Surgical Subcommittee has the intention to collaborate on a prospective protocol to report the work-up done in relation to staging and pretreatment planning plus the given treatment. The aim is also to promote more uniform management of cervical cancer patients in the Nordic countries in the future.

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References


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Supporting Information legend

Appendix S1. NSOG Surgical Subcommittee questionnaire on imaging diagnostics in the primary diagnostic work-up in cervical cancer.

Legend of Figure

Figure 1. T2 weighted sagittal (A), para-axial (B) and axial (C) pelvic magnetic resonance imaging (MRI) and whole-body fluorodeoxyglucose (FDG) positron emission tomography-computed tomography (PET-CT) (D-G) at primary diagnostic work-up in a 53-year-old patient diagnosed with squamous cell carcinoma, clinical FIGO stage IIB. MRI depicts a large cervical tumor (A; white arrows) with tumor extension into the upper ventral vaginal wall (black arrows) and disrupted stromal ring at the right side (B) indicating parametrial tumor invasion. Enlarged internal iliac lymph nodes (open arrows) are depicted with irregular architecture and boundaries at MRI (C) and with moderate FDG avidity at PET-CT (D), all suggesting lymph-node metastases. Primary tumor is highly FDG-avid (E, G), and the moderately FDG-avid retroclavicular left lymph node (F; open arrow) was histologically confirmed as metastatic. Pretreatment detailed knowledge of local tumor extent and metastatic lymph nodes enabled a tailored treatment strategy with primary internal and external radiation therapy and subsequent chemotherapy with carboplatin and paclitaxel. The patient had no signs of recurrence 4.5 years after primary diagnosis.

Table 1. The number of imaging modalities, multidisciplinary team meetings and sentinel lymph node procedures performed for pretreatment planning in patients with newly diagnosed cervical cancer cases, at 19 of 22 Nordic Gynecological Oncology Centers.
One center did oncologic treatment alone.

**Imaging Modalities (n=19)**

<table>
<thead>
<tr>
<th>Number of different imaging Modalities used at a center</th>
<th>Modality</th>
<th>Number of centers</th>
</tr>
</thead>
<tbody>
<tr>
<td>One imaging modality</td>
<td>PET-CT</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Up to three imaging modalities</td>
<td>US</td>
<td>9 (47)</td>
</tr>
<tr>
<td></td>
<td>MRI</td>
<td>18 (95)</td>
</tr>
<tr>
<td></td>
<td>PET-CT</td>
<td>15 (79)</td>
</tr>
<tr>
<td></td>
<td>CT</td>
<td>10 (53)</td>
</tr>
<tr>
<td>Four imaging modalities</td>
<td>US, MRI, PET-CT, CT</td>
<td>3 (16)</td>
</tr>
</tbody>
</table>

**Multidisciplinary Meetings (n=19)**

<table>
<thead>
<tr>
<th>Imaging presentation at Multidisciplinary meeting</th>
<th>Yes</th>
<th>18 (95)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No</td>
<td>1 (5)</td>
</tr>
</tbody>
</table>

**Surgical Procedure (n=18*)**

<table>
<thead>
<tr>
<th>Robotic-assisted radical hysterectomy</th>
<th>13 (72)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Robotic-assisted, laparoscopic and abdominal radical hysterectomy</td>
<td>5 (28)</td>
</tr>
</tbody>
</table>

**Sentinel Lymph Node (SLN) Procedure (n=18*)**

| Established practice                                   | 3 (17)       |
| In protocolled trial                                   | 5 (28)       |
| Established practice and in protocolled trial         | 1 (5)        |
| Not performed                                          | 9 (50)       |

*One center did oncologic treatment alone.

US, ultrasound; MRI, magnetic resonance imaging; PET-CT, positron emission tomography-computed tomography; CT, computed tomography

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Table 2. Summary of the cervical cancer guidelines recommendations for treatment, FIGO 2012 with amendment in FIGO 2015 and ESGO-ESMO-ESP 2017.

<table>
<thead>
<tr>
<th>FIGO stage</th>
<th>FIGO 2012</th>
<th>FIGO 2015</th>
<th>ESGO-ESMO-ESP 2017</th>
</tr>
</thead>
<tbody>
<tr>
<td>1A1</td>
<td>TAH, TLH or vaginal hysterectomy. <em>Fertility sparing, request no LVSI</em>; Cone biopsy with clear margins</td>
<td>Consider SLN procedure</td>
<td>Conization</td>
</tr>
<tr>
<td></td>
<td></td>
<td>If tumor &lt; 2 cm, cervical &amp; stromal invasion &lt;50% &amp; MRI/CT lymph node negative: Simple hysterectomy/trachelectomy + PLN/SLN procedure</td>
<td></td>
</tr>
<tr>
<td>1A2</td>
<td>Modified radical hysterectomy + PLN <em>Fertility sparing</em>; Large cone biopsy/radical trachelectomy + PLN</td>
<td>Conization or simple hysterectomy.</td>
<td>If +LVSI, consider SLN procedure</td>
</tr>
<tr>
<td>1B1</td>
<td>Modified radical hysterectomy + PLN</td>
<td>Chemo-radiation</td>
<td>Prevent the combination of radical surgery and radiotherapy. Intraoperative assessment of lymph nodes, SLN procedure + bulky nodes, frozen section if metastatic lymph nodes then disrupt surgery, and give chemo-radiation</td>
</tr>
<tr>
<td>1B2</td>
<td>Modified radical hysterectomy + PLN</td>
<td>Timely completion important</td>
<td></td>
</tr>
<tr>
<td>2A1</td>
<td>Post-operative high-risk indicates adjuvant chemo-radiation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2A2</td>
<td></td>
<td>PET-CT most accurate method for PAL metastasis.</td>
<td></td>
</tr>
<tr>
<td>&gt;2B</td>
<td></td>
<td>PET-CT most accurate method for PAL metastasis.</td>
<td></td>
</tr>
<tr>
<td>4A</td>
<td>No extension to the pelvic sidewall and/or fistula; consider primary pelvic exenteration</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: FIGO, International Federation of Gynecology and Obstetrics; ESGO-ESMO-ESP, European Society of Gynecological Oncology – European Society for Medical Oncology – European Society of Pathology; TAH, total abdominal hysterectomy; TLH, total laparoscopic hysterectomy; LVSI, lymph-vascular space invasion; PLN, pelvic lymph node excision; SLN, sentinel lymph node; MRI, magnetic resonance imaging; CT, computed tomography; PET-CT, positron emission tomography-computed tomography; PAL, para-aortic lymph nodes.