



# Neurogenic bladder in patients with cervical cancer after treatment

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Cervical cancer is still a global health burden worldwide, contributing to the fourth most common cancer in women in the world and a leading cause of cancer death of women in developing countries, although cervical cancer rates are dramatically decreasing overall among women in the United States, and Taiwan after an application of precancer screening strategies.<sup>1-5</sup> Despite of which cancer subtype and human papilloma virus (HPV) infection status, primary treatment with curative intent for women with cervical cancer consists of surgery (radical hysterectomy [RH] or radical trachelectomy), concurrent chemoradiation (CCRT), or a pretreatment therapy (neoadjuvant chemotherapy [NACT]) and a combination of these treatments; and in routine clinical practice, the treatment opinion is often based on the International Federation of Obstetrics and Gynecology (FIGO) cancer stage and sometimes according to the fertility consideration.<sup>1,2,6</sup> However, the complications of treatment either by surgery or by CCRT have persistent negative impacts on the physiological and psychological function of women. One of complications after treatment is pelvic floor dysfunction (PFD), which is a public health issue with significantly negative effects on quality of life (QoL).<sup>7-10</sup> Therefore, the issue addressing this topic is very important. In the October issue of the *Journal of the Chinese Medical Association*, Dr. Chou and colleagues used a Nationwide population-based database (Longitudinal Health Insurance Database [LHID] from the National Health Insurance Research Database [NHIRD]) to assess the risk of neurogenic bladder in women with cervical cancer after RH.<sup>11</sup>

The authors analyzed 39,793 women with cervical cancer after treatment, and the authors used an age- and index year-matched strategy to compare the risk of development of neurogenic bladder

of women who were treated with and without RH (17,936 in each group).<sup>11</sup> During 372,836 person-year follow-up period, a total of 1087 subjects have been complicated with neurogenic bladder (592 [3.3%] in the RH group and 495 [2.76%] in the non-RH group), contributing to adjusted hazard ratio (aHR) as 1.2 with 95% confidence interval (CI) of 1.1–1.4.<sup>11</sup> Furthermore, the women in the younger age group (age between 20 and 44 years) had a significantly increased risk of the development of neurogenic bladder after RH compared with those in women aged  $\geq 45$  years of age, and of most importance, patients over 65 years of age did not increase any risk of the development of neurogenic bladder.<sup>11</sup> The current study is interesting and worthy of further discussion.

Although the primary treatment with curative intent for women with early-stage cervical cancer can be easily separated into surgical and nonsurgical treatment, due to the anatomic relationship, any curative therapy for cervical cancer may result in damage to the organs surrounding the cervix with subsequent development of impaired their original function. Urinary bladder is located and attached to the anterior wall of the cervix and rectum is just attached to the posterior wall of the cervix and both of them are organs vulnerable to dysfunction after cervical cancer treatment. For example, RH, involving more extensive removal of the vagina, parametrial tissue, and uterosacral ligaments with damage to the autonomic nerve innervating the muscle of the bladder, urethral sphincter, and pelvic floor fasciae, together with pelvic lymph node dissection with interruption of patency of lymphatic drainage can provide a curative treatment for early stage cervical cancer with 88%–97% of the 5-year overall survival rate.<sup>9</sup> Additionally, radiotherapy, one major component of CCRT for cervical cancer treatment, can be utilized for the treatment of patients with any stage cervical cancer, although it is often applied to patients with locally advanced stage, such as FIGO IIB-IVA cervical cancer. Similar to RH, radiotherapy also directly or indirectly causes the damage of the urinary bladder and bowel, with subsequently developing radiation cystitis, radiation colitis, and other PFD as well as lower urinary tract symptoms (LUTS).<sup>10</sup> However, similar to other cancers from the female genital organs, the treatments for patients with cervical cancer may be more complicated, and many of them may need a combination of two or more strategies to improve the therapeutic outcome.<sup>10,12</sup> For example, patients after RH may also need post-operative CCRT treatment, contributing to uncertainty to know whether these complications are directly related to RH or biased by CCRT alone or combination. One multicenter retrospective study tried to evaluate pelvic organ function for patients with

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cervical cancer after treatment, and the results showed postoperative adjuvant therapy indeed increased the risk of PFD, such as stress urinary incontinence (SUI) with an odd ratio (OR) of 2.4 (95% CI 1.1–5.0) and overactive bladder syndrome (OAB) with an OR 1.5 (95% CI 1.0–2.4), respectively.<sup>10</sup> Although we do not know whether the increased risk of neurogenic bladder in women less than 65 years, and especially in women between 20 and 45 years may be confounded by postoperative adjuvant therapy after RH, the possibility is high. Therefore, Dr. Chou also clearly demonstrated its possibility as the limitation in their study.<sup>11</sup>

Additionally, as shown by authors, the different approach for RH or extent of radicality is significantly associated with PFD, including neurogenic bladder.<sup>11</sup> One critical and important issue about the QoL and oncology safety of women with cervical cancer after the use of modified approach based on less in place of the conventional exploratory or abdominal RH, such as minimally invasive surgery (laparoscopic and robotic approach) and nerve-sparing RH is still arguable and consensus is not in agreement for all gynecological oncologists.<sup>1,4,5,9</sup> Although the trend in use of less invasive procedures, including simple hysterectomy and the aforementioned modified approach for the management of early-stage cervical cancer may be increased,<sup>12</sup> much concern is present whether the “radicality (extent) of surgery” is adequate.<sup>12,13</sup> Dr. Sia used the National Cancer Database to review the case of women with FIGO stage IA2 and IB1 (<2 cm) cervical cancer between 2004 and 2015 and they found although simple hysterectomy did not influence the 5-year survival outcome for FIGO stage IA1 cancer (95.1% for RH and 97.6% for simple hysterectomy with HR of 0.70, 95% CI 0.41–1.20), 5-year survival was significantly better in women with FIGO IB1 treated with RH compared to that with simple hysterectomy (95.3% versus 92.4% with HR 1.55, 95% CI 1.18–2.03), suggesting the parametrial resection (parametrectomy) during hysterectomy (RH) is a critical procedure as the treatment of choice for women with FIGO stage IB1 cervical cancer.<sup>12</sup>

Moreover, Dr. Zapardiel further identified factor associated with voiding dysfunction after radical parametrectomy (similar to the meaning of RH), and found previous pregnancy and type of parametrectomy are independent factors associated with PFD, although PFD are temporary and the majority of the patients recover in less than 30 days.<sup>13</sup> Dr. Zapardiel’s finding found PFD is not influenced by surgical approach (open versus minimally invasive).<sup>13</sup> In China’s study, the authors found that minimally invasive RH, by contrast, increased the risk of all items of PFD, such as SUI (OR 1.6, 95% CI 1.1–2.2), urogenital distress inventory-6 (UDI-6, OR 1.2, 95% CI 1.1–1.2), colorectal anal distress inventory-8 (CRADI-8, OR 1.1, 95% CI 1.0–1.2), and OAB (OR 1.7, 95% CI 1.0–2.8).<sup>10</sup> It is interesting to find that minimally invasive RH involved in more extensive resection of cardinal ligament and uterosacral ligament (parametrectomy) and vaginal wall compared with conventional RH did, contributing to the exacerbated PFD in cervical cancer women after surgery. All suggest that radicality of RH may be a critical and determining factor associated with PFD. PFD increases the rates of urinary tract infection, hospital visits or admission, and patient’s dissatisfaction, showing a negative impact on patients’ QoL.<sup>14</sup>

The balance between benefits and risks for the treatment of potential life-threatening diseases, such as cervical cancer is always a dilemma. Any attempt to minimize the destruction of organs and the impairment of their associated functions cannot cross the safety of patients. Similarly, any extensive and traumatic

injury to provide an intent of curability of life-threatening diseases should be considered the future QoL. Understanding of the pathophysiology of diseases themselves and continuous improvement of technology and treatment methods are an essential part to provide a better QoL without compromising the therapeutic outcome in patients, regardless of which diseases are involved.<sup>15</sup>

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