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Lymphatic mapping and sentinel lymph node detection in women with cervical cancer

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Abstract

Lymphatic mapping and sentinel node detection have been applied to almost every solid tumor and sentinel node status have become part of the American Joint Commission on Cancer (AJCC) staging criteria in both breast cancer and malignant melanoma. As the presence of metastatic disease in lymph nodes is the most important prognostic factor on survival in women with cervical cancer, the ability to reliably detect sentinel nodes might triage women to adjuvant radiotherapy without the need for full lymphadenectomies and their associated morbidity. To date, multiple international investigators have performed single institution investigations with promising results. Overall, 831 women have been undergoing lymphatic mapping and sentinel node detection as part of their cervical cancer therapy as reported in the literature. Combining results from all these studies, a sentinel node was identified in 90% of cases with an overall sensitivity of detecting metastatic disease of 92% with an 8% false negative rate. The overall negative predictive value was over 97%. There remain controversies in moving forward with accepting sentinel node biopsy as the standard in treating women cervical cancer including 1) determining an acceptable false-negative rate, 2) establishing the importance of micrometastatic disease or isolated tumor cells in sentinel nodes, and 3) discovering the minimum number of cases a surgeon needs to become proficient in mapping techniques. Large, multi-institutional studies in both Europe and the United States are nearing completion and their results should help guide the future direction for sentinel node technologies in the treatment of cervical cancer.

Keywords: Sentinel node; Lymphatic mapping; Cervical cancer

Introduction

Metastatic disease to regional lymph nodes is consistently one of the most important therapeutic and prognostic factors in virtually every solid malignancy. The famous American surgeon William Halsted recognized this, incorporating lymph node dissection in the first radical mastectomy in 1882. For women with breast cancer, this extremely morbid approach included removing not only the breast and underlying tissue but also the regional axillary lymph nodes as well as the lymphatic channels and surrounding fibrous tissue.

About the same time in Europe, the French anatomist Marie Sappey was exploring the cutaneous lymphatic system in humans by injecting mercury into cadavers which allowed him to view routes of lymphatic drainage. Sappey noticed that lymphatic drainage was both *orderly* and *predictable*, an important tenet for sentinel node theory that would follow one hundred years later. In the middle of the twentieth century, surgeons recognized that cancer spread from primary lesion to lymph nodes by tumor emboli and not by progressively growing up the lymphatic channels. These findings set the stage for modern exploration of lymphatic mapping and sentinel node detection in solid malignancies.

The first to publish on these techniques was Ramon Cabanas whose 1977 landmark paper in sentinel node detection in men with penile cancer began the modern era with this approach [1]. By finding the lymphatic channel on the dorsum of the penis in men with distal cancers, Cabanas was able to cannulate the vessel injecting it with ethiodized oil, a radio opaque dye that

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could be seen on plain films of the groin. He was able to demonstrate that for these patients the sentinel node, defined as the first node draining the primary lesion and therefore the first site of tumor metastasis, was almost always located in the superficial inguinal nodes in the groin. This technique, however, required that the single draining lymphatic channel could be identified and cannulated, not typically attainable in most cancers.

In 1992, Donald Morton published his experience with sentinel nodes in patients with cutaneous melanoma [2]. His technique, which is essentially the basis for modern lymphatic mapping, involved injecting radiocolloid and vital blue dyes intradermally around the tumor allowing the microlymphatics of the skin to take up the compounds and transport them to the sentinel node. This technique did not require identification and cannulation of lymphatic channels and also had the additional benefit of identifying multiple basins or aberrant nodal drainage. These techniques have been explored in virtually every solid tumor and sentinel node status has become part of the American Joint Commission on Cancer (AJCC) staging criteria in both breast cancer and malignant melanoma.

Scientific relevance of sentinel nodes in cervical cancer

The node status in women with cervical cancer is the most important predictor of survival and often guides decisions for postoperative adjuvant radiotherapy. However, the vast majority of women with early stage cervical cancer (stages IA2 and IB1) will not have nodal disease thereby making complete lymphadenectomy unnecessary. For these women, the risks of intraoperative complications of this procedure such as vascular injury and hemorrhage as well as postoperative sequelae like lymphocyst formation and lymphedema are all for naught. For the remaining 15–20% of women who do have lymph node spread, complete retroperitoneal dissections and lymphadenectomy substantially increases postoperative radiation bowel complications by adhesion formation and tacking of small bowel in the radiation field. In addition, the combination of pelvic lymphadenectomy and radiotherapy significantly increases lymphedema of the lower abdomen, mons pubis, and lower extremity. Successfully proving and mastering sentinel node detection for women with cervical cancer could minimize risks for both patients with and without metastatic disease to the lymph nodes.

In addition, the identification of sentinel nodes allows for detection of micrometastatic disease as pathologists are able to focus their attention on the sentinel node, the basin most at risk for disease spread. This includes the addition of ultrasectioning and immunohistochemical staining of these nodes. To perform these diagnostic tests on all lymph nodes resected is too expensive and time intensive.

Review of literature

Table 1 reviews reports in the English literature of sentinel node detection in women with early cervical cancer. This table only includes those publications with >20 patients since a long-recognized limitation of lymphatic mapping is the higher rate of false-negative sentinel node detection in the first few cases a surgeon performs [3,4].

Table 1
Summary of published literature for lymphatic mapping in patients with cervical cancer

Author	Year	Patients	Technique	SN identified,%	Metastatic Disease,	Sensitivity,%	False negative,%	NPV,%
O'Boyle	2000	20	B	70	20	100	0	100
Dargent	2003	70	B	NR	27	100	0	NR
Marichole	2004	29	B	100	28	63	38	88
DiStefano	2005	50	B	90	20	90	10	97
Schwendinger	2006	47	B	83	21	90	10	97
Rob	2007	26	B/IB *	100	15	100	0	100
Malur **	2001	21	I	76	0	N/A	N/A	100
		20	IB	90	20	100	0	100
Van Dam	2003	25	LI	84	20	100	0	100
Angioli	2005	37	LI	70	16	100	0	100
Lin	2005	30	LI	100	23	100	0	100
Silva	2005	56	LI	93	30	82	18	92
Hauspy	2007	39	LI/LIB *	97	8	100	0	100
Buist	2002	25	LIB	100	40	90	10	94
Levenback	2002	39	LIB	100	21	88	12	97
Rhim	2002	26	LIB	100	19	80	20	96
Plante	2003	70	B/LIB *	94	22	100	0	100
Barranger	2004	36	LIB	92	12	100	0	100
Martinez-Palon	2004	25	LIB	90	15	100	0	100
Niikura	2004	20	LIB	83	22	86	14	95
Wydra	2006	100	LIB	100	10	100	0	100
Kushner	2007	20	LIB	87	17	100	0	100
Total		**831**		**89.8**	**20.5**	**91.8**	**8.2**	**97.3**

SN — sentinel node; NPV — negative predictive value; B — Blue dye only; I — intraoperative radiolabeled colloid; L — Preoperative lymphoscintigraphy; NR — not recorded; N/A — not applicable.

* These studies used combinations of blue dye and radiolabeled colloid but did not separate in published data.

** This study reported separate data for intraoperative radiolabeled colloid only and combined radiolabeled colloid/blue dye.