Exploring innovative nodal imaging and treatment strategies in breast cancer: a next step in patient tailored axillart treatment?

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Introduction

Breast cancer is the most common cancer among women worldwide, with 1.38 million newly diagnosed breast cancer patients in 2008. The highest incidence rates are reported in Western countries and in the Netherlands 14,000 women are diagnosed each year with breast cancer. Due to its high incidence, breast cancer has an important societal and economic impact in the Netherlands. Health care costs related to breast cancer are estimated to be 696 million euros annually.

Survival rates in breast cancer are still increasing, with a current 5-year overall survival of 88%, owing to better multidisciplinary treatment. Treatment consist of resection of the primary tumor and one or more axillary lymph nodes, and if indicated followed by a combination of hormonal-, chemo-, immuno- and/or radiotherapy. On the other hand, quality of life of survivors is affected by the morbidity caused by this treatment. Consequently, it is important to select patients that will benefit from the separate components of breast cancer treatment and to prevent exposure of patients to components of the treatment that do not positively affect their survival, while causing lifetime morbidity.

Relevance of scientific results in this thesis

This thesis addressed several topics on (re-)staging of axillary lymph nodes and the treatment of these nodes. For a long time the standard procedure to assess axillary lymph node status in breast cancer patients was axillary lymph node dissection (ALND). ALND is associated with significant short- and long-term morbidity. Most reported complications are seroma (15-75%), upper extremity lymph edema (20%), nerve injury (55-75%) and reduced shoulder function (16%). The psychological impact of lymphedema has been described to be as distressing as the initial diagnosis of breast cancer. Patients with breast cancer related lymphedema have been found to have a lower quality of life, a higher level of anxiety or depression, a higher likelihood of chronic pain and fatigue, and greater difficulty functioning socially and sexually compared to breast cancer patients without lymphedema.

In the past 15 years, the sentinel lymph node biopsy (SLNB) procedure has become the standard invasive technique to evaluate the nodal status in clinically node negative breast cancer patients. During a SLNB procedure, 1-2 axillary lymph node will be removed, compared to at least 10 axillary lymph nodes during an ALND. Complications known from the ALND still occur after SLNB, though less frequently; most reported are seroma, hematoma, lymphedema, numbness, tingling and pain. Severe lymphedema occurs in still 8% after a follow-up of 3 years.
To avoid unnecessary morbidity related to the treatment of the axillary lymph nodes, we evaluated the use of axillary ultrasound as a selection tool to direct patients to an ALND of SLNB. We showed that with the standard use of axillary ultrasound, some patients will be overtreated with ALND, and thus unnecessary exposed to possible long-term morbidity of this procedure. Therefore, we advised that for the current daily practice, the use of axillary ultrasound should be discussed for every patient individually.

Form other studies we learned that the detection and surgical removal of every metastatic lymph node is not mandatory anymore, without compromising overall survival. This creates new opportunities to avoid even the less invasive SLNB procedure in patients without lymph node metastases. It is assumed that axillary ultrasound is probably inaccurate to select the patients with node negative breast cancer, since we showed that still 16% with a negative axillary ultrasound would have macro metastatic disease. After studying multiple nodal (re-)staging techniques, we found that a gadofosveset-enhanced axillary MRI has the highest potential as a noninvasive method for nodal (re-)staging in patients with breast cancer. The use of gadofosveset-enhanced axillary MRI can probably eliminate overtreatment and minimize the morbidity of any invasive nodal staging procedure in breast cancer. This is also of economic value; besides sparing the costs of a SLNB procedure, the related costs to relieve the morbidity can also be saved. Nonetheless, results on this technique first have to be confirmed in future studies, before it can be implemented in the treatment of new breast cancer patients.

Target population

The results of thesis are relevant for patients with new diagnosed breast cancer. Further, it offers more information on axillary nodal staging and treatment consequences for clinicians involved in the multidisciplinary treatment of patients with breast cancer.

Innovation and Future

The use of gadofosveset enhanced axillary MRI for nodal staging in breast cancer is innovative. This contrast agent was originally developed for imaging blood vessels. Gadofosveset is very effective for its purpose, since it binds to albumin, and therefore remains in the vascular systemic for a prolonged period. Due to its affinity with albumin, it is also useful to image lymph nodes. Gadofosveset enhanced MRI has proven already is safety and efficacy in patients with rectal cancer. This thesis is the first that shows its also promising in breast cancer patients. Therefore, it is not unlikely that gadofosveset enhanced MRI could be useful in other tumor types, when the absence or presence of lymph node metastases determinates the treatment plan.
Future research should be conducted to confirm the diagnostic performance of gadofosveset-enhanced MRI on patient level in a larger group of patients with breast cancer, preferably in a multi-center setting. Ultimately, clinical outcome studies are needed to understand whether an NPV of 94% is oncologically safe to replace the current SLNB and ALND. The slightly lower NPV gadofosveset-enhanced axillary MRI could theoretically increase the risk of regional recurrences, yet this disadvantage could well balance against the treatment related morbidity associated with SLNB and ALND.