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2016

document version

Publisher's PDF, also known as Version of record

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citation for published version (APA)

Flach, G. B. (2016). *Minimally invasive diagnostics for occult lymph node metastases in head and neck cancer*. [PhD-Thesis - Research and graduation internal, Vrije Universiteit Amsterdam].

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CHAPTER 11

English summary



SUMMARY

Head and neck squamous cell carcinoma (HNSCC) is the 9th most common cancer worldwide. Subsites in HNSCC are the oral cavity, oropharynx, hypopharynx and larynx. The stage of disease is categorized in the TNM-classification system: the extent of the tumor (T), the presence of cervical lymph node metastases (N) and distant metastases (M). The TNM-stage is important since it determines the patients' treatment options. The status of the neck, whether lymph node metastases are present or not, is one of the most important prognostic factors. Staging the neck with conventional diagnostic methods is not accurate enough, particularly in patients with a clinically negative (cN0) neck. It is known that in patients with cT1-T2N0 oral squamous cell carcinoma the risk of occult (clinically undetectable) lymph node metastases is about 30%. Management of the neck in these patients, has therefore been subject of debate for years. The dilemma is to choose for elective neck dissection which means that occult lymph node metastases are removed, but that the majority (60-70%) of patients undergo unnecessary treatment. Or to choose for observation of the neck with the drawback that 30-40% of the patients develop delayed lymph node metastases. In an attempt to avoid unnecessary elective neck dissection, observation may be an acceptable option, unless early detection of delayed lymph node metastases is guaranteed. Ultrasound guided fine needle aspiration cytology (USgFNAC) has been the most reliable conventional technique in the detection of lymph node metastases and is easily repeated during follow-up to detect delayed metastases. Another solution for this debate may be more accurate staging at pretreatment.

Sentinel node biopsy (SNB) is a diagnostic method in which lymph nodes that are at highest risk to harbor metastases, are detected and meticulously histopathologically examined. If a metastasis is diagnosed in the sentinel node, the neck is in principle treated by a neck dissection. If the sentinel node is free of tumor, the neck will be observed during follow-up. More accurate staging of the cN0 neck, leads to individualized management of the neck.

The aim of this thesis was to assess the management of the cN0 neck in T1-T2 oral cancer patients by a minimal invasive diagnostic strategy. This was done by retrospective evaluation of the 'wait and scan' strategy by USgFNAC in terms of survival, evaluation of the use of sentinel node biopsy (SNB) to detect occult lymph node metastases in cN0 oral cancer patients, analysis of the effect of previous treatment on the use of SNB, evaluation of the additional value of late lymphoscintigraphic imaging, interobserver analysis of lymphoscintigraphic interpretation, assessment of the health-related quality of life and cost-effectiveness of a SNB based diagnostic strategy in oral cancer, and assessment of the feasibility of SNB in the larynx.

During the 1990s and early 2000s, before the introduction of SNB, careful observation of the USgFNAC negative neck has been the strategy in cT1-T2N0 oral cancer patients at VU University Medical Center (VUmc). This observational strategy was called 'wait and scan' (W&S), meaning strict surveillance by using USgFNAC of the neck during follow-up to detect delayed lymph node metastases early. Previous studies from VUmc have shown high salvage rates using this W&S strategy. We set out to report on survival data of this policy. The study described in **chapter 2** is a retrospective survival analysis of patients with cT1-T2N0 oral cancer who were treated by transoral excision and followed by the W&S strategy. The aim was to investigate the outcome of the observational W&S strategy. Of the 285 included patients, 234 had been followed by W&S and, as a reference, 51 patients had undergone elective neck dissection (END). Survival rates were compared between groups and correction for confounding factors was performed.

Of the W&S patients, 27.8% had delayed metastases and the 5-year disease-specific (DSS) and overall survival (OS) were 94.2% and 81.6%, respectively. W&S patients with delayed metastases had a 5-year DSS and OS of 80.0% and 62.8%, respectively. Of the patients who underwent END with a diagnosed metastasis, these figures were 81.3% and 64.2%, respectively. Between W&S and END patients, survival rates were not significantly different. Of the W&S patients with delayed metastases, 90.6% needed postoperative radiotherapy versus 55.0% of patients with positive END.

We concluded that a W&S strategy using strict USgFNAC surveillance is justified as survival is not negatively influenced. With this strategy unnecessary neck dissection and accompanying morbidity could be avoided in 72.2% of patients. For the small proportion of patients with delayed metastases more extensive treatment with adjuvant radiotherapy was needed. To minimize the proportion of patients needing more extensive treatment a more accurate preoperative diagnostic method to stage the cN0 neck is warranted.

In **chapter 3** the accuracy of SNB for staging of the cN0 neck in oral and oropharyngeal patients was evaluated. In a Dutch multicenter trial with 4 participating institutes, sixty-two patients with cT1-T2 oral and oropharyngeal cancer and N0 neck based on USgFNAC were included. All patients underwent preoperative lymphoscintigraphy and intraoperative gamma probe guidance to identify and detect the SN(s). SNB negative patients were carefully observed during follow-up and SNB positive patients were treated by subsequent neck dissection, radiotherapy or a combination of both. SNB detected lymph node metastases in 32% (20/62) of patients. Of the 42 patients with a SNB negative result, 5 developed delayed lymph node metastases, of whom 4 patients could be successfully salvaged. Disease-free (DFS), overall (OS) and disease-specific (DSS) survival of SNB negative patients were 72.0%, 92.7% and 97.4%, respectively. For SNB positive patients these numbers were 73.7%, 79.7% and 85.0%, respectively (DFS: $p = 0.916$, OS: $p = 0.134$, DSS: $p = 0.059$, respectively). With SNB the risk of occult lymph node metastases was reduced from 40 to 8%. A sensitivity of 80% and negative predictive value of 88% of SNB were found. Neck control rate was 97% in SNB negative and 95% in SNB positive patients.

This study revealed that SNB substantially reduces the risk of occult lymph node metastases in cT1-T2N0 oral cancer patients and enables excellent control of the neck.

It is known that previous treatment of the neck (e.g. neck dissection and/or (chemo)radiotherapy) may have influence on the lymphatics and may change or block original drainage patterns. Therefore, in case of a local recurrence or second primary tumor, therapy of the neck focusing on the neck levels at risk as it would be in the primary setting may not be appropriate. In **chapter 4** a prospective observational study was conducted to evaluate the clinical application of SNB in 22 oral cancer patients who were previously treated on the neck. Of the patients, 4/22 (18%) were previously treated only on the contralateral neck side. The SN detection rate was 100%, unexpected drainage was found in 25% of patients and 75% had a lymph node metastasis in the SN. The other 18 patients had ipsi- or bilateral previous neck treatment and a SN detection rate of 83%. In 7% of the patients the cN0 neck was upstaged by SNB, and 67% of the patients had unexpected lymphatic drainage patterns. The median follow-up was 22 months. Regional tumor control and negative predictive value were 100%.

Conclusions of this study were that SNB in previously treated oral cancer patients is feasible and reliable, and that regional tumor control after staging by SNB is excellent. SNB renders an assessment of the individual lymphatic drainage pattern, compensating for potential alterations after previous treatment of the neck.

In clinical practice, diagnostic imaging procedures should be useful and efficient. In **chapter 5** the clinical value of performing late lymphoscintigraphic imaging was questioned. For this study, lymphoscintigrams of 60 cT1-T2N0 oral cancer patients were retrospectively assessed. Both scans: early (directly following injection of ^{99m}Tc -nanocol and late (2-4h after injection) lymphoscintigrams were evaluated. Foci visible on late lymphoscintigrams were categorized: (a) no visualization of additional foci considered to be SNs; (b) additional foci visualized that are considered to be SNs and (c) foci visualized only during late imaging. Histopathological results of the harvested SNs were related to the corresponding foci.

In all 60 patients a focus visible on lymphoscintigram was identified as SN. Early imaging was able to visualize at least one focus in 51/60 (85%) patients, whereas in 9/60 (15%) patients only late imaging was able to visualize foci. In this latter group of patients most oral tumor sites were other than mobile tongue and floor of mouth (FOM). In paramedian and midline tumors, bilateral drainage was observed in the majority (83%) of tumors, with half of them only being visible during late imaging. In 14/51 (27%) patients, late imaging resulted in additionally visualized foci which were marked as SNs, resulting in a more extensive surgical procedure. With histopathological examination, no metastases were found in those SNs from additionally visualized foci. Therefore, it can be concluded that these additional foci visible on lymphoscintigraphy were clinically not relevant. Moreover, all SNs identified during early imaging correctly predicted whether the neck was positive or negative for cancer.

The results of this study indicated that additional late lymphoscintigraphic scans are only useful in patients with oral tumors located other than the mobile tongue and FOM, and in patients with paramedian or midline tumors. Based on these findings we suggested to perform late lymphoscintigraphy only in patients with oral cancer other than oral tongue and midline or paramedian tumors.

Adequate interpretation of the lymphatic drainage pattern is an essential step in the SNB procedure. In oral cancer, identification of the SN can be challenging if multiple foci are visible on lymphoscintigraphy. In **chapter 6** interpretation of lymphoscintigraphic imaging was assessed. To keep SNB accurate but minimal invasive, it is important to critically interpret the lymphoscintigram and distinguish the first echelon with true SNs from second echelon nodes. We performed an interobserver study to assess the interobserver variability in defining SNs on lymphoscintigrams of cT1-T2N0 oral cancer patients. Sixteen observers (head and neck surgeons, nuclear medicine physicians or teams of both) from various European institutes were asked to interpret lymphoscintigrams to select SNs of 9 patients with 47 foci (3-9 per patient) using a scale of 'yes/equivocal/no'. Interobserver variability was evaluated by kappa (K) analysis, using linear weighted pairwise comparison of the observers. Conservative (equivocal scored as no) and sensitive (equivocal considered as yes) assessment strategies were investigated using pairwise kappa analysis.

Interobserver variability of all cases using a 3-point scale showed fair agreement (71%, $K_w = 0.29$). The conservative and sensitive analyses both showed moderate agreement: conservative approach $K = 0.44$ (in 80% of the foci the observers agreed) and sensitive approach $K = 0.42$ (81% agreement). More foci and bilateral drainage resulted in lower agreement, whereas a multidisciplinary assessment (team of both) in image interpretation and a higher level of observer experience appeared to increase agreement.

The results of this study showed that among observers there is practice variation in defining SNs on lymphoscintigraphy with moderate interobserver agreement. To achieve higher agreement specific guidelines are warranted.

SNB has shown its value in accurate detection of occult lymph node metastases in oral and oropharyngeal cancer, whereas in other HNSCC sites SNB is still under investigation. In patients with laryngeal cancer and cN0 neck a total laryngectomy is usually combined with elective neck dissection(s). Based on the risk of occult lymph node metastases the decision whether to perform an elective neck dissection or not is difficult. In **chapter 7** the feasibility of SN identification and potential accuracy of SNB in laryngeal cancer patients undergoing total laryngectomy with elective neck dissection was investigated. During surgery 40MBq ^{99m}Tc -nanocoll was endoscopically injected around the tumor. Lymphoscintigraphy was not performed. We identified the SN ex vivo in the neck dissection specimen with a gamma probe. Histopathological examination of the neck dissection specimen served as reference test.

We included 19 patients, of whom 13 laryngeal cancer patients with untreated necks and 6 with prior neck treatment. SN identification was successful in 68.4% (13/19) and was significantly higher in patients with untreated necks (92.3% versus 16.7%, $p < 0.01$). In 4 of 13 (30.7%) patients with successful SN identification metastases were found and patients were upstaged by SNB. Sensitivity and negative predictive value were 80.0% and 87.5%, respectively.

This study revealed that SN identification in laryngeal cancer patients undergoing total laryngectomy is feasible in patients with untreated necks. Further studies are needed to determine the usefulness and accuracy of SNB in laryngectomy patients.

Health-related quality of life and psychological aspects of a therapy gain more interest. Of the study in **chapter 8** the primary aim was to evaluate prospectively the impact of a SNB based strategy (surveillance in SNB negative (SNB-) and subsequent neck dissection in SNB positive (SNB+) patients) in cT1-T2N0 oral cancer patients on the course of health-related quality of life, psychological distress and shoulder disability from diagnosis to 6 months follow-up. The secondary aims were to obtain insight into long-term shoulder functioning and into the preference of patients for an END strategy or a SNB based strategy.

A series of 52 patients (39 SNB-, 13 SNB+) completed the EORTC QLQ-C30 (quality of life-cancer module), QLQ-H&N35 (quality of life-head and neck cancer module), HADS (hospital anxiety and depression scale), IES (impact of event scale) and SDQ (shoulder disability questionnaire) questionnaires at baseline (before transoral excision and SNB), after SNB diagnosis, and at 6 months follow-up. Objective shoulder measurements were investigated after 2 years follow-up. Interviews on neck management strategies were conducted after 4.5 months follow-up.

The course of the mean scores on the QLQ-C30, QLQ-H&N35, HADS, IES and SDQ questionnaires over time was not significantly different between SNB- and SNB+ patients. Median IES subscale scores showed subclinical reactions. Results of SDQ increased significantly in SNB+ patients at 6 months follow-up, which partly recovered at late follow-up. At 2 years follow-up no significant differences in objective shoulder measurements were found, but SNB+ patients reported more often skin numbness of the neck. Most patients preferred a SNB based strategy over an END strategy.

With this study it can be concluded that the impact of a SNB based strategy in cT1-T2N0 oral cancer patients is comparable for SNB- and SNB+ patients (with subsequent neck dissection) in terms of HRQoL, psychological distress and shoulder functioning. Most patients preferred a SNB based strategy over an END strategy.

In **chapter 9** a cost-effectiveness study was performed. If a novel management strategy is proposed to become standard of care, it should preferably be cost-effective compared with previous management strategies. A model to calculate the cost-utility of different strategies for the detection of occult lymph node metastases in cT1-T2N0 oral cancer was created. A decision tree followed by a Markov model was designed to compare the cost-utility of the following strategies: (a) USgFNAC, (b) SNB, (c) USgFNAC and if negative, SNB and (d) END. Data were collected from 62 patients in four Dutch head and neck centers. Utilities were measured with the EQ-5D questionnaire and resource use was recorded from patient charts. Costs were calculated from a hospital perspective (2015 Euros). The cycle length was one year, with 5-year, 10-year and lifetime horizons. Uncertainty was explored with scenario analyses and probabilistic sensitivity analyses.

With a 5- or 10-year time horizon, SNB resulted in the highest number of additional quality-adjusted life years (QALYs, 0.12 and 0.26, respectively) for the smallest additional costs (€ 56 and € 74, respectively) compared with strategy (a) (USgFNAC). With a lifetime horizon END resulted in the highest number of additional QALYs (0.55) for an additional € 1,626 per QALY gained compared to USgFNAC. When making different assumptions regarding duration of disutility's (≥ 5 years) or improvement of sensitivity of SNB ($\geq 3\%$), SNB appeared to be the most favorable strategy from all time horizons.

The results of this study revealed that SNB is cost-effective in patients with cT1-T2N0 oral cancer. SNB may become the optimal strategy from all time horizons if its sensitivity could be slightly improved.