Minimally invasive staging of patients with melanoma: sentinel lymphadenectomy and detection of the melanoma-specific proteins MART-1 and tyrosinase by reverse transcriptase polymerase chain reaction

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Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Health technology
Reverse transcriptase polymerase chain reaction (RT-PCR) to detect messenger Ribonucleic Acid (mRNA) for tyrosinase, and Melanoma Antigen Recognised by T cells-1 (MART-1) were compared with routine histopathologic study to detect microscopic metastases in sentinel nodes.

Type of intervention
Diagnosis.

Economic study type
Cost-effectiveness analysis (cost-consequences).

Study population
The study population comprised patients who had melanomas more than 1mm thick or Clark's level IV (a measure of disease severity), in the upper extremity, lower extremity, trunk or head and neck and no clinical evidence of nodal involvement. The inclusion criteria were that the patients were able to tolerate sentinel node biopsy and wide excision of their melanomas under local anaesthesia.

Setting
Out-patient department in secondary care in the USA.

Dates to which data relate
The dates for the effectiveness evidence, resources used and price year were not reported.

Source of effectiveness data
Effectiveness data were derived from a single study.

Link between effectiveness and cost data
The authors did not report any details about the data used to generate costs and it is, therefore, not possible to determine whether retrospective or prospective costing was carried out on the same sample of patients used to collect effectiveness and cost data or a different sample.

Study sample
No power calculations were reported. Fifty patients with melanoma more than 1mm thick were included in the study. All patients underwent sentinel lymphadenectomy under local anaesthesia. After the sentinel nodes were identified they
were cut in half. Half of the node sample was sent for routine histopathologic study (n=50) and half of the node was preserved in liquid nitrogen for analysis by RT-PCR to detect mRNA for tyrosinase and MART-1 (n=50). The method of sample selection and details about patients who were excluded or who refused to participate in the trial were not reported. The authors suggested that the initial study sample was appropriate for the clinical study question because they stated that the patients must be suitable for local anaesthesia as part of the inclusion criteria.

**Study design**
This was a single-centre, non-randomised trial with concurrent controls. The duration of follow-up and loss to follow-up were not reported. No blinding was reported for the assessment of outcomes.

**Analysis of effectiveness**
The method of analysis for the clinical study was not stated. The primary outcome was positive detection of metastatic spread of melanoma.

**Effectiveness results**
A total of 106 sentinel nodes were harvested form the 50 patients. Ten patients had a total of 15 sentinel nodes that were positive for metastatic spread of melanoma by routine histopathologic examination and these were also positive by RT-PCR analysis for tyrosinase and MART-1. Three of the patients with positive lymph nodes had one more node each that was negative by histopathologic examination but positive by RT-PCR analysis (one was positive for tyrosinase and MART-1 and two positive for MART-1). Three patients with negative lymph nodes had one more node each that was negative by histopathologic examination but positive by RT-PCR analysis (two were positive for MART-1 and tyrosinase and one positive only for MART-1). No statistical analysis was reported.

**Clinical conclusions**
The authors’ concluded that the patients can tolerate lymphadenectomy from the head, neck, axilla and groin in an outpatient setting under local anaesthesia. Intraoperative lymph node preservation in liquid nitrogen is feasible. Both tyrosinase and MART-1 are promising markers in the detection of occult melanoma in lymph nodes.

**Measure of benefits used in the economic analysis**
No measure of benefits was used in the economic analysis. The authors did not establish whether selective lymphadenectomy as outpatient surgery with local anaesthesia is equivalent to the procedure conducted in the main operating theatre with general anaesthesia. The outcomes were reported in a disaggregated fashion and, as such, a cost-consequences analysis was conducted.

**Direct costs**
Quantities and costs were not analysed separately and the perspective of the study was not stated. The costs for carrying out lymphadenectomy in the main operating room under general anaesthesia (cost of the primary operation + pathology + secondary operations) or out-patient department under local anaesthesia (cost of the primary operation + secondary operation) were included. The authors measured the length of time required for the operation and recovery time and patients requiring admission for surgical or anaesthesia related complications. However, it was not clear whether or how these data were used in the estimation of costs. The authors reported that costs were estimated from charges for the operating room (for two hours), anaesthesia supplies, recovery room (two hours), and frozen-section examination performed intraoperatively.

A 60% accuracy rate on the frozen-section examinations was assumed and a 20% rate of positive sentinel nodes. The time horizon for the study was not reported. The methods used to measure resource use and estimate costs were not reported. The source of quantity/cost data was not reported. The dates when the quantity of resources were measured, and the price year were not reported. No discounting was reported, but the implicitly short time frame of the study (less than one-year) suggests it would not have been necessary.
Statistical analysis of costs
There was no statistical analysis of costs.

Indirect Costs
Indirect costs were not reported. No assessment can be made regarding whether this omission was valid due to the absence of the study perspective.

Currency
US dollars ($). No conversion rate was reported.

Sensitivity analysis
No sensitivity analysis was carried out.

Estimated benefits used in the economic analysis
The reader is referred to the effectiveness results reported earlier.

Cost results
The total cost for performing selective lymphadenectomy in the operating room was $206,654. The total cost for performing lymphadenectomy in the out-patient setting was $128,760.

Synthesis of costs and benefits
The costs and benefits were not combined.

Authors' conclusions
The authors concluded that RT-PCR analysis of nodal tissue for tyrosinase and MART-1 can detect melanoma and that it is a cost-effective method of staging patients with skin melanomas.

CRD COMMENTARY - Selection of comparators
The selection of comparators was unclear. The authors reported that a minimally invasive standard for selective lymphadenectomy had not been established and reported alternative approaches in use at the time of the study. These were:

outpatient surgery under local anaesthetic, permanent section examination and a subsequent operation for complete lymphadenectomy in patients with positive diagnosis of metastatic disease and

surgery in the main operating theatre using general anaesthetic and frozen section examination of the lymph nodes during surgery.

If the results were positive a complete lymphadenectomy was performed before the patient left the operating theatre. However, the authors did not compare selective lymphadenectomy in outpatient surgery using local anaesthetic to selective lymphadenectomy in the main operating theatre under general anaesthetic to establish a minimally invasive standard. The authors noted that routine histological examination of samples may not detect microscopic metastases in sentinel nodes. They described the alternatives as:

RT-PCR techniques, and
serial sectioning and immunohistochemical staining.

The authors described the latter technique as labour intensive, but did not indicate whether it is a rarely used technique, or whether there is evidence about relative effectiveness to justify excluding it from the study and comparing RT-PCR techniques to routine histological examination alone. You, as a user of this database, need to consider whether the alternatives compared are relevant to routine practice in your own setting.

Validity of estimate of measure of effectiveness
The study design was a prospective trial with concurrent controls which the authors described as a phase II study. As noted above, the authors did not compare the effectiveness of different methods of selective lymphadenectomy in the trial or by systematic review or analysis of existing evidence. This was not appropriate for the research aim to establish a standard for minimally invasive lymphadenectomy. The authors did not report whether power calculations were used to estimate the sample size or whether there was any statistical analysis of data. It is not possible to assess whether the differences between the diagnostic tests were due to chance or whether they were statistically significant.

Validity of estimate of measure of benefit
No summary measure of effectiveness was reported. The authors described the content of the histopathologic and RT-PCR findings in terms of positively identifying metastatic spread of melanoma. The benefit in terms of the effect on the survival and health of the patient was not reported. The authors acknowledged that patient preferences and tolerance of selective lymphadenectomy under local anaesthesia may vary, but did not go on to evaluate this.

Validity of estimate of costs
The costs reported in this paper compare the process of conducting lymphadenectomy under general anaesthesia in the main operating room and under local anaesthesia in the out-patient setting. It was not clear whether these costs related directly to the process of using RT-PCR analysis of nodal tissue for tyrosinase and MART-1 rather than histopathologic analysis to detect metastatic spread of melanoma. The authors did not report sufficient information to enable the validity of the cost estimates to be assessed.

Other issues
The authors compared the results of their study with other published evidence and suggested that the results of the study were consistent with the literature reviewed. Limited information was reported about the design and conduct of the study and analyses. No statistical or sensitivity analyses were conducted to test the robustness of the results. These factors, combined with the choice of comparators, mean it is not possible to assess whether the study was internally or externally valid or robust.

CRD Commentary
This stated aim of this paper was to establish a minimally invasive standard for sentinel lymphadenectomy. This included an evaluation of the feasibility of using RT-PCR analysis of nodal tissue for tyrosinase and MART-1 to detect microscopic metastases in sentinel nodes in an out-patient setting. It did not set out to evaluate the cost-effectiveness of this intervention.

Implications of the study
The authors reported that they had demonstrated the feasibility and accuracy of lymph node preservation in liquid nitrogen and the detection of metastatic spread using RT-PCR techniques. The authors recommend further research to determine whether there is a survival advantage in treating patients with minimal nodal disease compared to those with more extensive disease, and to determine whether patients with histopathologically negative disease, but RT-PCR positive disease, have a worse prognosis.
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None stated.

Bibliographic details

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Other publications of related interest

Indexing Status
Subject indexing assigned by NLM

MeSH
Actins /analysis; Ambulatory Surgical Procedures /economics; Anesthesia, Local; Antigens, Neoplasm /analysis; Biomarkers, Tumor /analysis; Cost-Benefit Analysis; Female; Humans; Lymph Nodes /chemistry /pathology; Lymphatic Metastasis /diagnosis; MART-1 Antigen; Male; Melanoma /economics /pathology /surgery; Monophenol Monoxygenase /analysis; Neoplasm Proteins /analysis; Neoplasm Staging; Polymerase Chain Reaction; RNA-Directed DNA Polymerase; Skin Neoplasms /economics /pathology /surgery

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