Management strategies for stage IB2 cervical cancer: a cost-effectiveness analysis

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
Three strategies to treat Stage IB2 squamous cell carcinoma of the cervix (CXCA) were considered:

radical hysterectomy with pelvic and para-aortic lymphadenectomy followed by tailored chemoradiation therapy (CTRT) for high-risk patients (RHYST);

primary CTRT for all patients; and

neoadjuvant chemotherapy followed by radical hysterectomy with pelvic and para-aortic lymphadenectomy with tailored CTRT for high-risk patients (NAC).

In the RHYST strategy, patients received 45 Gy fractionated into 25 treatments followed by 8 additional boost treatments to the pelvis for a total of 60 Gy. They also received 5 weekly treatments of cisplatin chemotherapy (40 mg/m2), beginning the first day of whole pelvic radiation therapy (WPRT). In the primary CTRT strategy, patients received 45 Gy of WPRT fractionated into 25 treatments with 3 additional boost treatments to the parametrium for a total of 50.4 Gy. They also received 5 weekly treatments of cisplatin chemotherapy (40 mg/m2), beginning the first day of WPRT. In the NAC strategy, patients underwent primary chemotherapy consisting of 4 cycles of weekly cisplatin, bleomycin and vincristine chemotherapy.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised a hypothetical cohort of patients with Stage IB2 CXCA.

Setting
The setting was secondary care and a hospital. The economic study was carried out in the USA.

Dates to which data relate
The effectiveness data were derived from studies published between 1980 and 2002. No dates were explicitly reported for resource use. The price year was 2003.

Source of effectiveness data
The effectiveness evidence was derived from a synthesis of completed studies.
Modelling
A decision tree model was constructed to assess the costs and 5-year disease-free survival (DFS) associated with the three treatment strategies in a hypothetical cohort of 10,000 women.

In the RHYST strategy, patients underwent radical hysterectomy with pelvic and para-aortic lymphadenectomy. The patients had three potential possibilities. Specifically, no further therapy, aborted surgery for evidence of advanced disease followed by primary chemoradiation, and tailored chemoradiation for high-risk factors. The patients received adjuvant CTRT if they had positive surgical margins, parametrial involvement, or positive lymph nodes. The same three possible branches were considered in the NAC strategy. In all strategies, a small percentage of patients received adjuvant CTRT with extended-field para-aortic radiation therapy.

The structure of the tree was reported. All patients had a computed tomography (CT) scan of the abdomen and pelvis to rule out obvious advanced disease. A separate decision analysis model evaluating a hypothetical cohort of 10,000 patients was created with the same three strategies (RHYST, CTRT, NAC) to establish complication rates, including haematologic, gastrointestinal, genito-urinary, cardiovascular, neurologic and cutaneous complications. The time horizon of this model was 5 years.

Outcomes assessed in the review
The outcomes estimated from the literature were:

the probabilities of 5-year DFS with no further therapy, adjuvant chemoradiation, adjuvant chemoradiation (plus para-aortic boost), aborted RHYST with primary chemoradiation, aborted RHYST with primary chemoradiation (plus para-aortic boost) in both the RHYST and NAC branches; and

the probabilities of 5-year DFS with primary chemoradiation in the CTRT branch.

The corresponding rates in the complication model were also reported.

The probabilities of 5-year DFS The incidence of aborted surgery with Stage IB2 disease and the percentage of patients that would require adjuvant CTRT after radical hysterectomy were reported.

Study designs and other criteria for inclusion in the review
A review of the literature was undertaken to identify the primary studies. An attempt was made to use data from Phase III trials. However, when these data were not available, Phase II data or clinical experience were used.

Sources searched to identify primary studies
Not reported.

Criteria used to ensure the validity of primary studies
Not reported.

Methods used to judge relevance and validity, and for extracting data
Not reported.

Number of primary studies included
Twenty-one primary studies provided the clinical data.

Methods of combining primary studies
A narrative method appears to have been used to combine the primary estimates.

**Investigation of differences between primary studies**
Not reported.

**Results of the review**
In the RHYST branch, the probabilities of 5-year DFS were as follows:
- no further therapy, 70%;
- adjuvant chemoradiation, 70%;
- adjuvant chemoradiation (plus para-aortic boost), 50%;
- aborted RHYST with primary chemoradiation, 70%; and
- aborted RHYST with primary chemoradiation (plus para-aortic boost), 50%.

In the CTRT branch, the probability of 5-year DFS was 70% with primary chemoradiation.

In the NAC branch, the probabilities of 5-year DFS were as follows:
- no further therapy, 70%;
- adjuvant chemoradiation, 70%;
- adjuvant chemoradiation (plus para-aortic boost), 50%;
- aborted RHYST with primary chemoradiation, 70%; and
- aborted RHYST with primary chemoradiation (plus para-aortic boost), 50%.

In the complication model, the probabilities of complications in the RHYST branch were as follows:
- no further therapy, 5%;
- adjuvant chemoradiation, 40%;
- adjuvant chemoradiation (plus para-aortic boost), 50%;
- aborted RHYST with primary chemoradiation, 30%; and
- aborted RHYST with primary chemoradiation (plus para-aortic boost), 40%.

In the complication model, the probability of complications with primary chemoradiation in the CTRT branch was 25%.

In the complication model, the probabilities of complications in the NAC branch were as follows:
- with no further therapy, 15%;
- adjuvant chemoradiation, 50%;
- adjuvant chemoradiation (plus para-aortic boost), 60%;
aborted RHYST with primary chemoradiation, 40%; and
aborted RHYST with primary chemoradiation (plus para-aortic boost), 50%.

The incidence of aborted surgery with Stage IB2 disease was 10%.

The proportion of patients that would require adjuvant CTRT after radical hysterectomy was 40%.

**Measure of benefits used in the economic analysis**
The summary benefit measure used was the cure rate, which was defined as 5-year DFS. This was estimated using the decision model.

**Direct costs**
The cost analysis was performed from the perspective of a third-party payer. It included all direct medical costs associated with the three treatment strategies, such as:

- initial cervical cancer evaluation (initial office visit, cervical biopsy, pathology fees and CT scan);
- RHYST (preoperative tests such as laboratory tests, electrocardiogram, and chest X-ray; operating room time and supplies, surgeon fees, anaesthesiology fees, pathology fees, post-anaesthesia care unit fees, and fees for a 3-day hospital stay);
- NAC (all costs for RHYST plus the costs of 4 treatments of weekly cisplatin, bleomycin and vincristine chemotherapy, including the costs for the chemotherapy agents, infusion costs, laboratory tests, intravenous fluids, and associated support medications such as antiemetics and steroids); and
- aborted radical hysterectomy with subsequent chemoradiation, primary CTRT, adjuvant CTRT and WPRT.

The costs of treating complications were not considered. The unit costs were presented in detail, whereas the quantities of resources used were provided for only a few items. The source of the resource use data was unclear. Direct costs rather than charges were used in the analysis and local charges were adjusted using a cost-to-charge ratio of 60%. The costs came from the University of Alabama at Birmingham and from average wholesale prices. Discounting was not relevant since the costs were incurred during a short timeframe. The price year appears to have been 2003.

**Statistical analysis of costs**
The costs were treated deterministically.

**Indirect Costs**
The indirect costs were not considered in the economic evaluation.

**Currency**
US dollars (§).

**Sensitivity analysis**
Several univariate sensitivity analyses were performed to assess the impact of variations in model assumptions on the estimated cost-effectiveness results. Variations in the rate of 5-year DFS, the costs of CTRT and the probability of receiving adjuvant CTRT were explored. The ranges of values were derived from published estimates using plausible ranges.
Estimated benefits used in the economic analysis
The cure rates (5-year DFS) were 69% with RHYST, 69.3% with NAC and 70% with CTRT.

Cost results
In a cohort of 10,000 patients, the estimated costs were $284 million with RHYST, $299 million with NAC and $508 million with CTRT.

Synthesis of costs and benefits
Average and incremental cost-effectiveness ratios were calculated to combine the costs and benefits of the alternative treatment strategies.

The average cost per cured patient was $41,212 with RHYST, $43,197 with NAC and $72,613 with CTRT.

The incremental analysis revealed that NAC was slightly more effective than RHYST. It yielded 30 more survivors per 10,000 patients, but at an additional cost of $15 million. This resulted in a cost of $499,783 per additional survivor.

CTRT was also more effective than RHYST. It yielded 100 more survivors per 10,000 patients, but at an additional cost of $224 million. This resulted in a cost of $2,240,000 per additional survivor.

The separate model showed that all three treatments had similar complications rates (22% for NHYST, 25% for NAC and 27% for CTRT).

The sensitivity analysis showed that the base-case results remained robust to variations in some clinical and economic data. For example, RHYST remained more cost-effective in comparison with NAC until the 5-year DFS of RHYST fell below 63%. The 5-year DFS of RHYST would have to fall below 10% in order to become less cost-effective than CTRT. RHYST remained the most cost-effective strategy even when the 5-year DFS of CTRT exceeded 99%.

Authors' conclusions
Radical hysterectomy with pelvic and para-aortic lymphadenectomy followed by tailored chemoradiation therapy for high-risk patients (RHYST) represented the most cost-effective treatment for patients with Stage IB2 cervical cancer (CXCA) in the USA.

CRD COMMENTARY - Selection of comparators
The authors stated that the treatments considered in the study were all possible strategies for the treatment of patients with Stage IB2 CXCA. You should decide whether they are valid comparators in your own setting.

Validity of estimate of measure of effectiveness
The effectiveness evidence came from a synthesis of published studies. However, no information on the methods or conduct of the review was provided. In addition, since details of the design and characteristics of the primary studies were not reported, it was not possible to assess the validity of the primary studies. The issue of the comparability of the primary estimates was not addressed, and only some key clinical variables were varied in the sensitivity analysis.

Validity of estimate of measure of benefit
The summary benefit measure used in the cost-effectiveness analysis was specific to the disease considered in the study. However, it should be reasonably comparable with other cancer-related interventions. No discounting was applied to extended survival.

Validity of estimate of costs
The costs included were consistent with the perspective adopted in the study. The authors stated that the costs of complications were not included in the analysis because of the lack of data. However, similar complication rates were observed across the treatment branches, thus the relative ranking of the interventions should not have been affected by the inclusion of such costs. The unit costs were reported for most items. The source of the costs was reported, but information on resource consumption was less clear. The costs were treated deterministically, but the impact of using alternative cost estimates was investigated in the sensitivity analysis. The price year was provided, which will facilitate reflation exercises in other time periods.

Other issues
The authors did not compare their findings with those from other studies. They also did not explicitly address the issue of the generalisability of the study results to other settings. In effect, the external validity of the analysis was low, although some sensitivity analyses were performed on key model estimates. Also, in the sensitivity analysis it was unclear which threshold was used to assess the cost-effectiveness of one strategy versus another. The authors stated that a possible limitation of their analysis was the narrowness of its scope, but the decision model attempted to reflect typical treatment patterns for the specific group of women with Stage IB2 CXCA.

Implications of the study
The study results supported the use of RHYST for the treatment of women with Stage IB2 CXCA.

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None stated.

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Other publications of related interest


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