Development of an evidence-based algorithm for the management of cervical cancer

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Summary

Objective: To develop a description of the management of cervical cancer to support locally developed, regional guidelines and to identify the level of primary research evidence to support it.

Design: Development of a flow-charted algorithm, using regional guidelines and clinician consensus. A Medline literature search for primary research was done to validate the algorithm and selection of papers, to verify if they were valid according to pre-defined criteria and to compare algorithm management with an alternative.

Main Outcome Measure: The highest level of evidence for algorithm management was based on the design of the supporting research.

Results: Twenty percent of the algorithm is supported by level I evidence (randomised controlled trials), 70% by level II evidence (cohort studies) and 10% by level IV evidence (expert opinion or case series).

Level II evidence supports the management of Stage Ia, squamous cell carcinoma by cone biopsy or a simple hysterectomy. This level of evidence also applies to research on the management of Stages Ib-IIa, by radical hysterectomy and pelvic lymphadenectomy followed by radiotherapy, if the lymph nodes are positive. Radiotherapy to treat Stages IIb-IV cervical cancer is supported by level I evidence. The management of Stage I adenocarcinoma is supported by level II evidence.

Conclusions: Evaluations of the effect of informing clinicians of the strengths of the proposed management are now required, as constructing evidence-based algorithms is worthwhile, only if they are likely to affect clinical practice.

Key words: Cervical cancer; Clinical algorithm; Evidence-based medicine.

Introduction

The five-year survival from cervical cancer in England and Scotland, UK, was 10% lower than the best in Europe for women diagnosed between 1978 and 1985 [1]. Recent cancer registry data for the South East of England shows a variation of approximately 20% in five-year survival between the highest and lowest rates [2]. Whilst a component of this variation may be due to the presenting stage of cancer, which is itself affected by age and socio-economic status [3], it is likely that gynaecological practice also plays a part [4-6]. An audit in the South East of England identified the variation in management of cervical cancer and demonstrated a significant, independent adverse effect on survival of under- or over-appropriate treatment [7]. The frequency of appropriate staging was 15.6% and appropriate treatment upon 59%, as judged against regionally agreed upon guidelines.

In common with other guidelines, those used in this South East of England audit may be criticised because of a failure to state how the evidence used in their creation was gathered and assessed [8]. Evidence-based medicine is the explicit and judicious use of the current best evidence in making decisions about the care of individual patients. It seeks to convert clinically important information about practice into answerable questions, to track down the best evidence with which to answer them, to critically appraise the evidence and to apply the results [9] and is an appropriate tool for improving a guideline.

The UK National Health Service Executive (NHSE) published written guidelines for those commissioning gynaecological cancer services [10]. They make recommendations about the management of cervical cancer, based on a series of wide ranging systematic reviews. Guidelines such as these have been criticised as poor tools for the busy clinician because they are too non-specific [11]. A flow chart has been shown to be better than written guidelines for imparting hospital policy to a variety of clinical and clerical staff. There was a reduction in the time taken to absorb and use the new information, as well as the number of errors committed by the users [12]. Clinical algorithms, presented as flow charts, have been evaluated as successful aids in diagnosis [13], determination of prognosis [14, 15] and therapy [16, 17].

In this paper we develop a flow-chart clinical algorithm to describe the gynaecological management of biopsy-diagnosed cervical cancer by adding decision making information to written recommendations derived from

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existing regional guidelines. We use the techniques of evidence-based medicine to find the highest level of primary research that supports each clinical action in the algorithm.

Methods

The guidelines for the management of cervical cancer, distributed to all gynaecologists before the audit in the South East of England [7], were updated in 1997 at meetings of the gynaecologists working in the health region. They recommended which investigations and surgical procedures should be performed but made no mention of the decisions required as a consequence.

The authors grouped the clinical investigations and surgical procedures in the guidelines according to the decision about the care that followed. An algorithm was constructed describing what clinical procedures should precede a decision and what actions should follow. It was presented as a flow chart and distributed to all the gynaecologists in the South East of England for comment on its feasibility and whether any alterations should be made. No changes were suggested by the 63% (29/46) of responding clinicians who manage gynaecological cancers.

The algorithm showed that the management of cervical cancer may be determined from knowledge of stage, histological type and whether fertility is to be preserved. For each of the different management pathways, Medline searches identified papers published between 1966 and 1998, excluding review articles and those not in the English language. The search strategies sought randomised controlled trials [18] or cohort studies [19] regarding radiotherapy, chemotherapy, hysterectomy, lymphadenectomy and conization for cervical cancer. Since the choice of therapy was dependant on the stage of disease, an additional search assessed the impact of correct staging on survival by looking for cohort studies on neoplasm staging [19].

Based on abstracts and titles articles were selected which purported to measure survival or disease-free survival after comparing the algorithm's suggested management with any other technique, when applied to the same categories of women, taking account of stage. The full text of these papers was judged, according to the criteria suggested by Sackett [9] and if valid, a level of evidence was assigned according to a hierarchy of evidence adapted from that proposed by the NHS Centre for Reviews and Dissemination [20]. Level I is used for randomised controlled trials and level II-1 for non-randomised controlled trials. Level II-2 applies to concurrently controlled cohort studies; subcategories 'A' and 'B' distinguish prospective and retrospective studies. Level II-3 indicates case-control studies. Level III is used for comparisons of case series with and without intervention, showing a large difference and Level IV is used for single case series, audits or the opinion of respected experts.

Papers supported the algorithm pathway if they showed that the recommended management offered either a better or no worse outcome than the alternative. If they opposed the algorithm management, they were reviewed with the gynaecological oncologists and the algorithm was modified accordingly.

Results

Figure 1 shows the first part of the algorithm for the management of cervical cancer, which covers the treatment of Stages IIb-IV. Figure 2 presents the management of Stages I-IIa. Figure 3 explains the symbols used.

Staging

No papers assessed the impact of inappropriate staging of cervical cancer on survival. One paper by Wolfe *et al.* [7] showed that the likelihood of appropriate staging investigations being performed was associated with the type of hospital at which the patient was managed, with teaching hospitals most likely to carry out all the necessary tests. The independent effect of inappropriate staging on survival was not assessed although worse survival was associated with inappropriate management. This study was graded II-2A.

Management of Stage Ia, squamous cell carcinoma

Table 1 summarises the evidence for the management of Stage Ia squamous cell carcinoma. From Medline two retrospective cohort studies (level II-2B) showed that the method of surgical management had little bearing on the almost 100% survival rate.

Management of Stages Ib1-IIa

Table 1 also summarises the evidence derived from valid cohort studies or randomised controlled trials about the management of Stages Ib and IIa, found using Medline. Cohort studies were included because they provided evidence about surgery as well as whether to use adjuvant therapy for women at high risk of recurrence.

From Medline retrospective cohort studies (level II-2B) showed that radical hysterectomy and pelvic lymphadenectomy offered a better prognosis than alternative surgical procedures but a randomised controlled trial showed that radiotherapy offered the same survival as radical surgery (level I). There is no benefit from extending lymphadenectomy to the para-aortic region (level II-2B). Disease-free survival and mortality was improved by treating women with positive pelvic lymph nodes with radiotherapy postoperatively (level II-2B). Three randomised trials (level I) showed that if adjuvant treatment was offered to women at high risk of recurrence, there was no survival benefit to be gained from using alternatives to radiotherapy alone. No evidence could be found regarding survival or disease-free survival after radical trachelectomy.

Management of Stages IIB-IV

Table 2 summarises the key features of the ten randomised controlled trials, found using Medline, which supported the algorithm and compared primary radiotherapy with another technique.

Six randomised controlled trials investigated the sequential use of chemotherapy before or after radiotherapy and showed no difference in survival or a significantly worse survival. Four studies investigated the concurrent use of chemotherapy with radiotherapy and showed no survival benefit. The most important deficiency of all these studies was an examination of whether they had sufficient power to detect a difference in outcome.

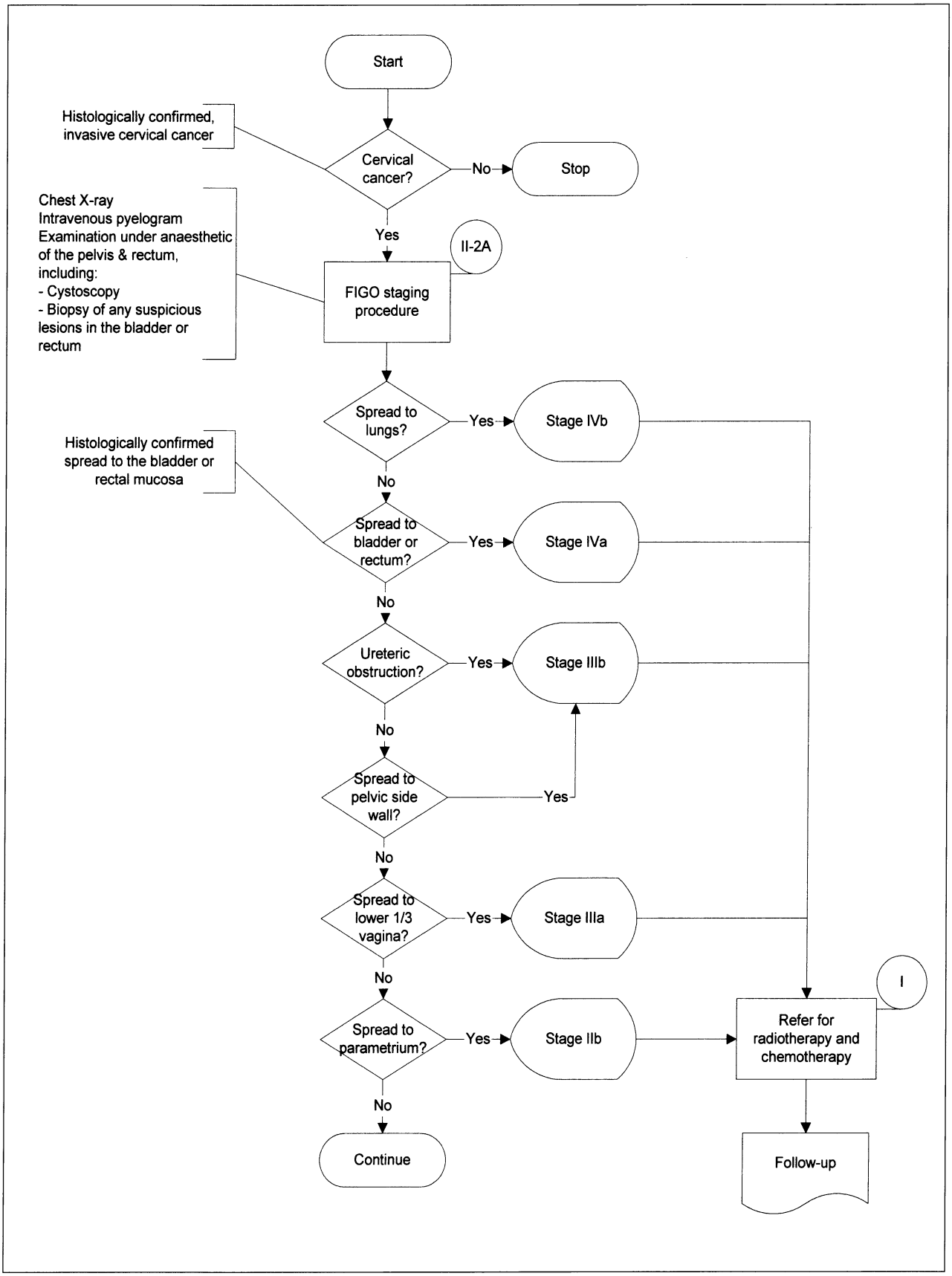

Figure 1. — Cervical cancer - staging & management of Stages IIb-IV.

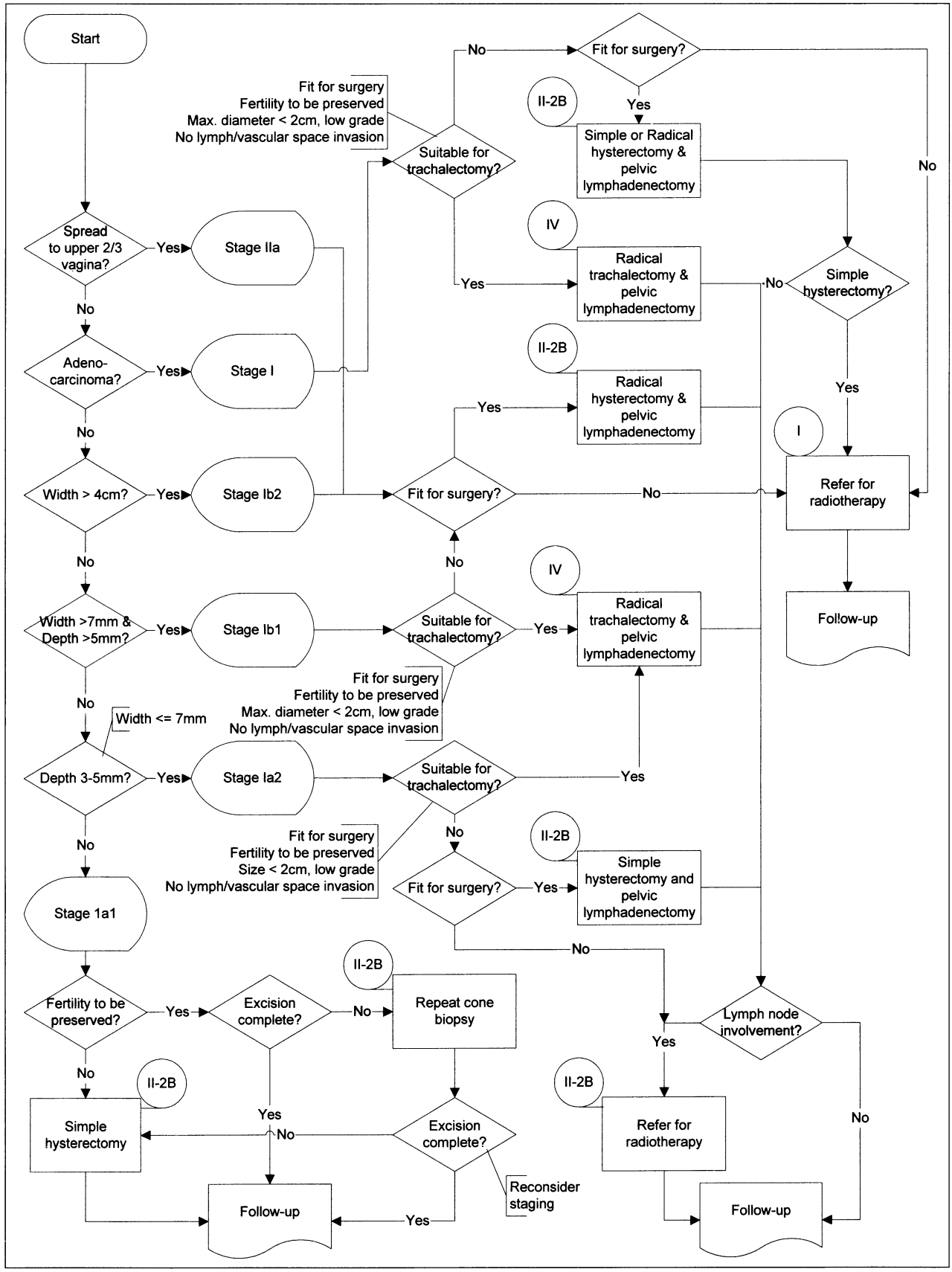

Figure 2. — Cervical cancer - staging and management of Stages I-IIa.

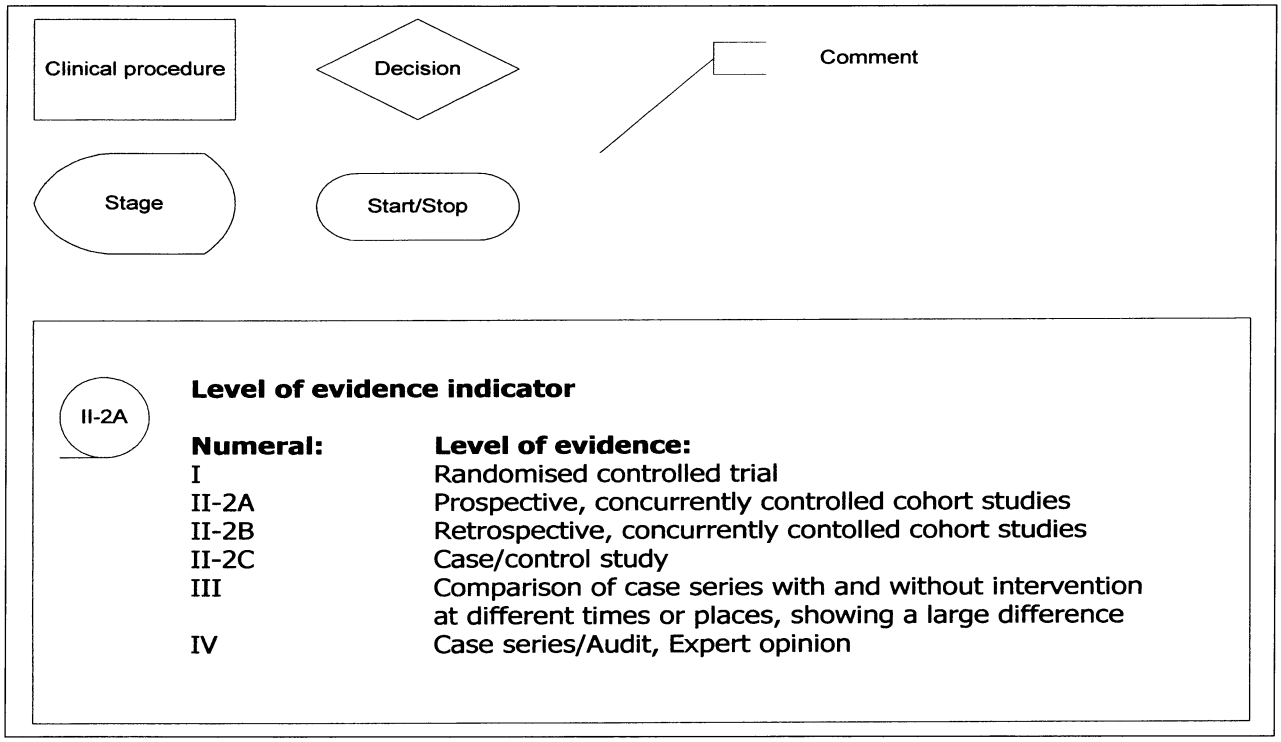

Figure 3. — Key to the symbols used in the flow-charts.

Table 1. — *The Medline evidence for algorithm management of Stage Ia and Ib-IIa cervical cancer.*

First Author	Year	n=	Level of evidence	Validity	Conclusions
Bissett D.	1994	420	II-2B		Women undergoing a variety of treatments (cone biopsy, simple and radical hysterectomy) for Stage Ia cervical cancer had 100% survival [4].
Kolstad P.	1989	643	II-2B	No adjustment for confounding variables	No deaths after at least three years of observation were observed among women undergoing cone biopsy, a simple hysterectomy, a radical hysterectomy or radiotherapy for Stage Ia cervical cancer. Four deaths were observed due to cervical cancer among those undergoing extended hysterectomy [29].
Bissett D.	1994	420	II-2B	Method of randomisation not reported. No sample size calculation.	Women undergoing non-radical hysterectomy have a worse survival than women undergoing radical hysterectomy, allowing for age, histology, grade and nodal status [4].
Landoni F.	1997	337	I		Radical surgery and pelvic lymphadenectomy with post-op radiotherapy if there is a high risk of recurrence has the same survival as radical radiotherapy [25].
Kinney W.	1998	185	II-2B		Women undergoing radiotherapy for positive pelvic lymph nodes post Wertheim hysterectomy and pelvic lymphadenectomy have a significantly better disease-free survival but no better mortality than matched controls undergoing the surgery only [30].
Lai C.	1999	891	II-2B		Women with lymp-node metastases post Wertheim's hysterectomy who were given adjuvant treatment had a better survival than those undergoing surgery only in a multivariate analysis [31].
Ayhan A.	1990	278	II-2B	No adjustment for confouding variables.	Women undergoing radical hysterectomy and pelvic lymphadenectomy receive no benefit if para-aortic lymphadenectomy is performed as well [32].
Kikkawa F.	1993	177	I	Method of randomisation not reported. No sample size calculation.	Addition of OK432 to radical hysterectomy, pelvic lymphadenectomy and radiotherapy confers no five-year survival benefit [33].
Curtin J.	1996	89	I	Method of randomisation not reported. No sample size calculation.	The addition of chemotherapy to radiotherapy offers no survival benefit for women with a high risk of recurrence [34].
Tattersall M.	1992	71	I	No sample size calculation.	The addition of chemotherapy to radiotherapy offers no survival benefit for women with positive pelvic lymph nodes [35].

Table 2. — *The Medline evidence for algorithm management of Stage IIb-IV cervical cancer.*

First Author	Year	n=	Level of evidence	Validity	Conclusions
Kigawa J.	1996	50	I	Method of randomisation not reported. No sample size calculation.	Neoadjuvant chemotherapy followed by surgery for responders confers no 3-year survival advantage over radiotherapy [36].
Chiara S.	1991	64	I	Method of randomisation not reported. No intention to treat analysis. No sample size calculation.	Neoadjuvant chemotherapy and radiotherapy confers no 3-year survival advantage over radiotherapy [37].
Souhami L.	1991	107	I	Method of randomisation not reported. No intention to treat analysis.	Radiotherapy and chemotherapy significantly worsens 5-year survival compared with radiotherapy [38].
Tattersall M.	1995	260	I	No sample size calculation.	Chemotherapy then radiotherapy significantly worsens 3-year survival compared with radiotherapy [39].
Sundfor K.	1996	94	I	Method of randomisation not reported. No sample size calculation.	Neoadjuvant chemotherapy followed by radiotherapy offered no better 3-year survival than radiotherapy [40].
Leborgne F.	1997	97	I	Method of randomisation not reported. No sample size calculation.	Neoadjuvant chemotherapy and radiotherapy confers no 5-year survival benefit over radiotherapy [41].
Thomas G.	1998	105	I	Method of randomisation not reported. No sample size calculation.	Concurrent 5-FU or hyperfractionated radiotherapy confers no survival advantage over radiotherapy [42].
Tseng C.	1997	122	I	Method of randomisation not reported. No sample size calculation.	Concurrent chemo and radiotherapy offer no 3-year survival advantage over radiotherapy [43].
Wong L.	1989	64	I	Method of randomisation not reported. No sample size calculation.	Weekly or twice weekly chemotherapy and radiotherapy confers no 5-year survival benefit over radiotherapy [44].
Overgaard J.	1989	331	I	Method of randomisation not reported. No sample size calculation.	Misonidazole concurrent with radiotherapy offers no survival advantage over radiotherapy [45].

Management of cervical adenocarcinoma

On searching Medline, one retrospective cohort study (level II-2B) compared radical surgery and radiotherapy if there were risk factors for recurrence with other forms of management and suggested there would be a better survival [21]. A second study showed that for Stage I patients, radical surgery offered a better prognosis than patients treated with radiotherapy in a multivariate analysis allowing for stage, grade, tumour size and cell type (22).

Overall, of ten clinical recommendations made by the algorithm two (20%) have level I evidence in their support, one (10%) has level II-2A evidence supporting it, six (60%) have level II-2B evidence supporting them and one (10%) has level IV evidence in its favour.

Discussion

Using electronic databases alone to find evidence has been shown to identify only half of the relevant literature; contacting an expert network and hand searching journals for references may be used to improve coverage [23]. A busy clinician will have Medline and review articles as sources of the literature but the value of each of these sources for evidence-based medicine is unknown.

In preparing for this paper, Embase was searched in addition to Medline, using similar keywords to find review articles about the management of cervical cancer. Examining the abstracts of the citations of these 45 review articles showed that whereas searches of Medline identified 1,344 articles of which 88 articles compared algorithm management with alternatives, 79 of 1,690 review article citations were relevant of which 27 articles had already been found by the Medline searches, yielding 62 new articles. From the abstracts of these articles, none increased the level of evidence nor added new information. This suggests little extra benefit from widening the search.

Although Medline identified more relevant studies than the search for review article references, neither source was efficient in terms of the time consuming steps - the total number of abstracts and papers read. For the application of evidence-based medicine, where the emphasis is on making the best use of relevant and valid evidence, Medline was judged likely to be the most effective source of research literature.

Almost all decisions regarding the primary management of cervical cancer are dependent on the appropriate determination of stage. The algorithm begins by requiring that gynaecologists carry out the necessary tests to comply with the International Federation of Gynaecological Oncologists (FIGO) [24] staging procedure. Understaging is avoided by systematically eliminating the possibility of distant spread, spread in the parametria to the pelvic side wall and to the lower third of the vagina.

The UK National Health Service Executive (NHSE) has recently published good practice guidelines on commissioning cancer services [10]. Although these are intended to guide purchasers of health services, they will be used by clinicians to guide their management [11]. The results of the literature searches concur with the NHSE guidelines that the impact of inadequate staging on survival cannot be assessed directly from the available research, however level II-2A evidence that inappropriate management adversely affects survival is available and this is associated with a low rate of appropriate staging.

Regarding the management of Stage Ia to IIa disease, the algorithm agrees with the NHSE guidelines that when invasion is less than 3 mm, hysterectomy can be avoided and, that deeper invasion ought to be managed with hysterectomy and pelvic lymphadenectomy. The algorithm supplements their conclusions with level II-2B evidence that postoperative radiotherapy, if the patient has risk factors for recurrence, will increase disease-free survival and with level I evidence that radiotherapy and chemotherapy offer no advantage over radiotherapy. On the basis of the same randomised trial comparing radiotherapy with surgery and radiotherapy [25], the algorithm is in agreement that radiotherapy is an option for women who are not suitable for surgery.

Precise assessment of the size of the tumour is useful in determining whether radical trachelectomy is viable for women wishing to preserve their fertility. It is appropriate to refer women with incomplete families and early-stage disease to a specialist centre experienced in this technique, especially as no evidence could be found regarding survival after this procedure.

Conclusions from comparisons of different surgical management options, using the retrospective cohort study design, may be affected by unmeasured confounding variables, missing data or failure to fully enumerate all cases. We suggest that it should be possible to improve this level of evidence for surgical management, by means of prospective concurrent data collection.

A recently published randomised controlled trial showed improved survival when chemotherapy combined with radiotherapy was compared with radiotherapy alone as primary treatment of Stage Ib cervical cancer [26]. Both arms of the trial were utilized following initial treatment. Although this study made no direct comparison with the proposed management of the algorithm, it strengthens the case that management of cervical cancer should involve close cooperation between oncologists and gynaecologists.

Regarding the management of higher stage disease and using neoadjuvant chemotherapy, we concur with the NHSE guidelines that the data are inconclusive. In our study, the validity of relevant papers was assessed using criteria suggested by Sackett *et al.* [9], which were chosen because they were aimed at clinicians. These suffer from the disadvantage that no account is taken of the power to detect an outcome, leading to the selection of evidence that failed to publish an assessment of the adequacy of sample size. Since four out of our six studies were also reported by Melville *et al.,* it is possible that the lack of power is part of the reason for the failure to reach a conclusion.

The failure to select studies of adequate potential may explain why the results of our search were inconclusive regarding concurrent chemotherapy for the management of Stages IIb-IV cervical cancer. Recently two large randomised trials demonstrated that there may be an advantage to using concurrent cisplatin chemotherapy with radiotherapy for women with Stage IIb-IV disease [27, 28]. They were published after the search was concluded. The algorithm recommends referral to an oncologist for radiotherapy. This recommendation could be changed to: "Refer for radiotherapy and chemotherapy".

Conclusions

The algorithm is a more succinct presentation than written guidelines and potentially more suitable for a busy clinician because it is specific to the management of the disease [11]. Levels of evidence from primary research can provide an estimate of the strengths of the proposed management. Evaluations of whether this form of presentation affects clinical management are required.

References

[1] Gatta G., Sant M.: "Survival of Cancer Patients in Europe: The EUROCARE Study". Lyon: IARC Scientific Publications; 1995; 2, Guide to tables, 278.

[2] Thames Cancer Registry. Matthews G. (ed.) Cancer in South East England 1996. London: Thames Cancer Registry, 1997, 1, Gynaecol. Cancer: Cervix, 7.

[3] Lamont D. W., Symonds R. P., Brodie M. M., Nwabineli N. J., Gillis C. R.: "Age, socio-economic status and survival from cancer of the cervix in the west of Scotland 1980-1987". *Br. J. Cancer*, 1993, *67*, 351.

[4] Bissett D., Lamont D. W., Nwabineli N. J., Brodie M. M., Symonds R. P.: "The treatment of stage I carcinoma of the cervix in the west of Scotland 1980-1987". *Br. J. Obstet. Gynaecol.*, 1994, *101* (7), 615.

[5] Jackson S., Murdoch J., Howe K., Bedford C., Sanders T., Prentice A.: "The management of cervical cancer in the South West Region of England". *Br. J. Obstet. Gynaecol.*, 1997, *104,* 140.

[6] Covens A., Rosen B., Gibbons A., Osborne R., Murphy J., DePetrillo A. *et al.*: "Differences in the morbidity of radical hysterectomy between gynecological oncologists". *Gynecol. Oncol.*, 1993, *51*, 39.

[7] Wolfe C. D., Tilling K., Bourne H. M., Raju K. S.: "Variations in the screening history and appropriateness of management of cervical carcinoma in South East England". *Eur. J. Cancer,* 1996, *32*A (7), 1198.

[8] Sudlow M., Thomson R.: "Clinical guidelines: quantity without quality". *Quality in Health Care*, 1997, *6*, 60.

[9] Sackett D. L., Richardson W. S., Rosenberg W. *et al.:* Churchill L., (ed.) "Evidence Based Medicine: How to Practice and Teach EBM". 1st London: Churchill-Livingstone, 1997.

[10] Melville A., Eastwood A., Kleijnen J.: NHS CRD (ed.). "Guidance on Commissioning Cancer Services: Improving Outcomes in Gynaecological Cancers. The Researh Evidence". London: NHS Executive, 1999.

[11] Sikora K.: "Cancer survival in Britain. is poorer than that of her comparable European neighbours". *B. M. J.*, 1999, *319*, 462.

[12] Guterman J. J., Mankovich N. J., Weinstein S., Picken B.: "Structured knowledge representation: an improved methodology for communication of hospital policy". Proceedings - the Annual Symposium on Computer Applications in Medical Care, 1995, 733.

[13] Franklin R. C., Spiegelhalter D. J., Macartney F. J., Bull K.: "Evaluation of a diagnostic algorithm for heart disease in neonates". *B. M. J.*, 1991, *302,* 935.

[14] Aitchison T. C., Sirel J. M., Watt D. C., MacKie R. M.: "Prognostic trees to aid prognosis in patients with cutaneous malignant melanoma". *B. M. J.*, 1995, *311*, 1536.

[15] Darbar D., Gillespie N., Choy A. M., Lang C. C., Pringle S. D., Pringle T. H. *et al.*: "Diagnosing left ventricular dysfunction after myocardial infarction: the Dundee algorithm". *QJM,* 1997, *90* (11), 677.

[16] Marsden A. K., Ng A. G., Dalziel K., Cobbe S. M.: "When is it futile for ambulance personnel to initiate cardiopulmonary resuscitation?". *B. M. J.*, 1995, *311*, 49.

[17] Foster G. R., Goldin R. D., Main J., Murray-Lyon I., Hargreaves S., Thomas H. C.: "Management of chronic hepatitis C: clinical audit of biopsy based management algorithm". *B. M. J.*, 1997, *315*, 453.
[18] McKibbon K. A., Walker-Dilks C. J.: "Beyond ACP Journal Club: How to harness MEDLINE for therapy problems". ACP Journal Club 1994, 121 (Suppl. 1), A10.
[19] McKibbon K. A., Walker-Dilks C. J., Haynes R. B., Wilczynski N., Beyond A. C. P.: "Journal Club: How to harness MEDLINE for prognosis problems". ACP Journal Club, 1995, 123 (Suppl. 1), A12.
[20] NHS CRD: National Health Service Centre for Reviews & Dissemination (ed.). "Undertaking Systematic reviews of Research on Effectiveness: CRD Guidelines for Those Carrying Out or Commissioning Reviews". York: York Publishing Services, 1996.
[21] Piura B., Dgani R., Yanai-Inbar I., Cohen Y., Glezerman M.: "Adenocarcinoma of the uterine cervix: a study of 37 cases". *J. Surg. Oncol.*, 1996, *61* (4), 249.
[22] Chen R. J., Chang D. Y., Yen M. L., Lee E. F., Huang S. C., Chow S. N., Hsieh C. Y.: "Prognostic factors of primary adenocarcinoma of the uterine cervix". *Gynecol. Oncol.*, 1998, *69* (2), 157.
[23] McManus R. J., Wilson S., Delaney B. C., Fitzmaurice D. A., Hyde C. J., Tobias R. S. *et al.*: "Review of the usefulness of contacting other experts when conducting a literature search for systematic reviews". *B. M. J.*, 1999, *317*, 1562.
[24] International Federation of Gynecology and Obstetrics: Pettersson F., Creasman W. T., Shepherd J. *et al.* (eds.). Annual Report on the Results of Treatment in Gynaecological Cancer. Stockholm: International Federation of Gynecology and Obstetrics, 1994.
[25] Landoni F., Maneo A., Colombo A., Placa F., Milani R., Perego P. *et al.*: "Randomised study of radical surgery versus radiotherapy for stage Ib-IIa cervical cancer". *Lancet*, 1997, *350* (9077), 535.
[26] Keys H. M., Bundy B. N., Stehman F. B., Muderspach L. I., Chafe W. E., Suggs C. L. *et al.*: "Cisplatin, radiation and adjuvant hysterectomy compared with radiation and adjuvant hysterectomy for bulky stage Ib cervical carcinoma". *N. Engl. J. Med.*, 1999, *340* (15), 1154.
[27] Morris M., Eifel P. J., Lu J., Grigsby P. W., Levenback C., Stevens R. E. *et al.*: "Pelvic radiation with concurrent chemotherapy compared with pelvic and para-aortic radiation for high risk cervical cancer". *N. Engl. J. Med.*, 1999, *340* (15), 1137.
[28] Rose P. G., Bundy B. N., Watkins E. B., Thigpen J. T., Deppe G., Maiman M. *et al.*: "Concurrent cisplatin-based radiotherapy and chemotherapy for locally advanced cervical cancer". *N. Engl. J. Med.*, 1999, *340* (15), 1144.
[29] Kolstad P.: "Follow-up study of 232 patients with stage Ia1 and 411 patients with stage Ia2 squamous cell carcinoma of the cervix (microinvasive carcinoma)". *Gynecol. Oncol.*, 1989, *33* (3), 265.
[30] Kinney W. K., Alvarez R. D., Reid G. C., Schray M. F., Soong S. J., Morley G. W. *et al.*: "Value of adjuvant whole-pelvis irradiation after Wertheim hysterectomy for early-stage squamous carcinoma of the cervix with pelvic nodal metastasis: a matched-control study". *Gynecol. Oncol.*, 1989, *34* (3), 258.
[31] Lai C. H., Hong J. H., Hsueh S., Ng K. K., Chang T. C., Tseng C. J. *et al.*: "Preoperative prognostic variables and the impact of postoperative adjuvant therapy on the outcomes of Stage IB or II cervical carcinoma patients with or without pelvic lymph node metastases: an analysis of 891 cases". *Cancer*, 1999, *85* (7), 1537.
[32] Ayhan A., Tuncer Z. S.: "Effect of paraaortic lymphadenectomy on 5-year survival in early stage cervical cancer". *Australian & N. Zealand J. Obstet. Gynaecol.*, 1990, *30* (4), 378.
[33] Kikkawa F., Kawai M., Oguchi H., Kojima M., Ishikawa H., Iwata M. *et al.*: "Randomised study of immunotherapy with OK-432 in uterine cervical carcinoma". *Eur. J. Cancer*, 1993, *29A* (11), 1542.
[34] Curtin J. P., Hoskins W. J., Venkatraman E. S., Almadrones L., Podratz K. C., Long *et al.*: "Adjuvant chemotherapy versus chemotherapy plus pelvic irradiation for high-risk cervical cancer patients after radical hysterectomy and pelvic lymphadenectomy (RH-PLND): a randomized phase III trial". *Gynecol. Oncol.*, 1996, *61* (1), 3.
[35] Tattersall M. H., Ramirez C., Coppleson M.: "A randomized trial of adjuvant chemotherapy after radical hysterectomy in stage Ib-IIa cervical cancer patients with pelvic lymph node metastases". *Gynecol. Oncol.*, 1992, *46* (2), 176.
[36] Kigawa J., Minagawa Y., Ishihara H., Itamochi H., Kanamori Y., Terakawa N.: "The role of neoadjuvant intraarterial infusion chemotherapy with cisplatin and bleomycin for locally advanced cervical cancer". *Am. J. Clin. Oncol.*, 1996, *19* (3), 255.
[37] Chiara S., Bruzzone M., Merlini L., Bruzzi P., Rosso R., Franzone P. *et al.*: "Randomized study comparing chemotherapy plus radiotherapy versus radiotherapy alone in FIGO stage IIB-III cervical carcinoma. GONO (North-West Oncologic Cooperative Group)". *Am. J. Clin. Oncol.*, 1994, *17* (4), 294.
[38] Souhami L., Gil R. A., Allan S. E., Canary P. C., Araujo C.M., Pinto L. H., Silveira T. R.: "A randomized trial of chemotherapy followed by pelvic radiation therapy in stage IIIB carcinoma of the cervix". *J. Clin. Oncol.*, 1991, *9* (6), 970.
[39] Tattersall M. H., Lorvidhaya V., Vootiprux V., Cheirsilpa A., Wong F., Azhar *et al.*: "Randomized trial of epirubicin and cisplatin chemotherapy followed by pelvic radiation in locally advanced cervical cancer. Cervical Cancer Study Group of the Asian Oceanian Clinical Oncology Association". *J. Clin. Oncol.*, 1995, *13* (2), 444.
[40] Sundfor K., Trope C. G., Hogberg T., Onsrud M., Koern J., Simonsen E., Bertelsen K., Westberg R.: "Radiotherapy and neoadjuvant chemotherapy for cervical carcinoma. A randomized multicenter study of sequential cisplatin and 5-fluorouracil and radiotherapy in advanced cervical carcinoma stage 3B and 4A". *Cancer*, 1996, *77* (11), 2371.
[41] Leborgne F., Leborgne J. H., Doldan R., Zubizarreta E., Ortega B., Maisonneuve J. *et al.*: "Induction chemotherapy and radiotherapy of advanced cancer of the cervix: a pilot study and phase III randomized trial". *Internat. J. Rad. Oncol., Biol., Physics,* 1997, *37* (2), 343.
[42] Thomas G., Dembo A., Ackerman I., Franssen E., Balogh J., Fyles A., Levin: "A randomized trial of standard versus partially hyperfractionated radiation with or without concurrent 5-fluorouracil in locally advanced cervical cancer". *Gynecol. Oncol.*, 1998, *69* (2), 137.
[43] Tseng C. J., Chang C. T., Lai C. H., Soong Y. K., Hong J. H., Tang S. G., Hsueh S.: "A randomized trial of concurrent chemoradiotherapy versus radiotherapy in advanced carcinoma of the uterine cervix". *Gynecol. Oncol.*, 1997, *66* (1), 52.
[44] Wong L. C., Choo Y. C., Choy D., Sham J. S., Ma H. K.: "Long-term follow-up of potentiation of radiotherapy by cis-platinum in advanced cervical cancer". *Gynecol. Oncol.*, 1989, *35* (2), 159.
[45] Overgaard J., Bentzen S. M., Kolstad P., Kjoerstad K., Davy M., Bertelsen K. *et al.*: "Misonidazole combined with radiotherapy in the treatment of carcinoma of the uterine cervix". *Internat. J. Rad. Oncol., Biol., Physics*, 1989, *16* (4), 1069.

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