What outpatient models have proven efficacy for assessment and management of pelvic radiotherapy late effects?

Palliative and Supportive Care Research Development

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Review Methods

Search Strategy: A systematic search was conducted across a wide-ranging set of databases: Ovid Medline, including In-Process & Other Non-Indexed Citations, Ovid Embase, Ebsco CINAHL and Cochrane Library.
The preliminary search strategy was developed on Ovid Medline using both text words and medical subject headings from January 2006 to February 2017 restricted to English language and humans. The search strategy was modified to capture indexing systems of the other databases. (Search strategies available upon request).

To identify additional papers, electronic tables of content for the last two years of the following journals were scanned:
- *British Journal of Cancer*
- *British Journal of Radiology*
- *International Journal of Gynaecological Cancer*
- *Journal of Endometriosis and Pelvic Pain Disorders*
- *Journal of Radiotherapy in Practice*
- *Radiotherapy and Oncology*

Furthermore reference lists of systematic reviews were checked for any relevant studies.
The searches generated 138 citations after removing duplicates and irrelevant records. Thirty eight full-text articles were assessed for eligibility.
Figure 1 represents the flow of information through the different phases of the review.

Inclusion:
Any service models or tools that have been used to detect and manage pelvic radiotherapy late effects.

Exclusion: Studies set in non-Organization for Economic Cooperation and Development (OECD) countries; Case series studies consisting of less than 25 patients; non-english language studies

Study selection/Quality Assessment/Data Extraction: Study selection was based upon review of the abstract by two independent reviewers. The full text was then assessed independently using a pre-designed eligibility form according to inclusion criteria. Any discrepancies between the two reviewers were resolved by consensus or by recourse to a third reviewer.

Context

Pelvic radiotherapy has an essential role in the curative treatment plan of several cancers, but is associated with late adverse effects which may persist for years and have significant impact on social functioning and quality of life. These late effects include gastrointestinal symptoms, urinary symptoms and psychosexual symptoms amongst others.

These symptoms often go unreported by patients, with the focus in busy clinical oncology settings often on disease control. However there is evidence that many gastroenterology symptoms can be managed by addressing the physiological and functional changes induced by radiotherapy, and opportunities may also exist for improving urological and sexual function.

The purpose of this rapid review is to identify models of care which accurately identify patients with late toxicity following pelvic radiotherapy, and effectively manage that symptom burden. The purpose is to inform the development of local services which can most efficiently address these currently unmet needs.

Key Findings

Despite the severity and frequency of symptoms, only one randomised controlled trial was identified testing an intervention suite to manage late bowel toxicity following pelvic radiotherapy (Andreyev et al). The study demonstrated that use of a defined algorithm (The Royal Marsden algorithm) allowed accurate symptom identification and assessment, and the use of an associated management plan improved bowel symptoms at six months when implemented by either a gastroenterologist or nurse practitioner.

There were no randomised studies identified of interventions directed at urological or sexual dysfunction following pelvic radiotherapy.

Two additional papers assessing the use of patient reported screening tools were identified: the first analysing subjective items from the LENT SOMA questionnaire (Barraclough et al) and the second the development of a short 3 question screening tool: ALERT-B (Taylor et al). Either might be used to screen patients in busy clinical settings. However the length of the LENT questionnaire may limit use. The ALERT-B tool is designed as a screening tool only and not as an outcome measure to assess response to intervention.

There is a lack of agreement on which outcome measures should be used to monitor treatment responses.

Key Findings continued

A. Reliability of evidence

The only interventional study (ORBIT trial, Andreyev et al) was a randomised trial. The reporting of the trial followed Consort guidelines and the statistical plan was clearly described. Allocation bias was minimized but there may have been selection bias as patients were selected from a radiotherapy list generated by the hospital and method of approach was variable. More men than women were randomised and age range differed between groups. By its nature, the study was unblinded to patients and intervention teams. Although outcome measures were largely patient reported, it was not clear who collected the follow up data, with risk of outcome bias if those collecting data were unblinded or involved in the treatment intervention. The level of missing data, or how that was handled, was not reported.

The prospective study of the LENT SOMA-derived questionnaire (Barraclough et al) reported toxicity data over a three year period but reliability of results is limited by the high dropout rate and low number of completed questionnaires particularly in years 2 and 3. The degree of missing data was not reported.

The psychometric component of ALERT-B validation (Taylor et al) was undertaken only in men with prostate cancer. The small number of questions may influence the reliability of some of the validation testing. Data missingness was reported as less than 2 percent.

B. Consistency of evidence

Patients in the ORBIT study (Andreyev et al) were stratified at randomization for tumour type and degree of bowel dysfunction with similar numbers in each group. The Royal Marsden algorithm was consistently applied across the intervention groups with quality assurance assessed for both the nurse and gastroenterologist application of the algorithm.

The prospective cohort in the LENT SOMA questionnaire study (Baraclough et al) were heterogeneous in terms of the dose of radiotherapy received, whether or not they had had surgery and the underlying tumour type and were assessed as a single group in terms of toxicity reporting.

C. Relevance of evidence

The ORBIT study (Andreyev et al) was undertaken in a single institution which already had a well established clinic for assessing and managing late bowel effects of pelvic radiotherapy. However the algorithm is designed for use by general gastroenterologists, and the associated descriptive paper by Benton et al identifies key competencies and clinical challenges for implementation by nurse practitioners, supporting its external use.

Although the refinement of the LENT SOMA-derived questionnaire (Barraclough et al) was based on data from a single institution, the data was derived from a cohort with a range of gynaecological malignancies treated in a standard fashion and should therefore be applicable to the wider community receiving pelvic radiotherapy.

The ALERT-B tool (Taylor et al) was validated in a restricted patient group (men with prostate cancer) but appeared to correlate well with bowel items of the Gastroenterology Symptom Rating Scale. It had good face validity in cognitive interviews and was easily administered in busy clinical settings.

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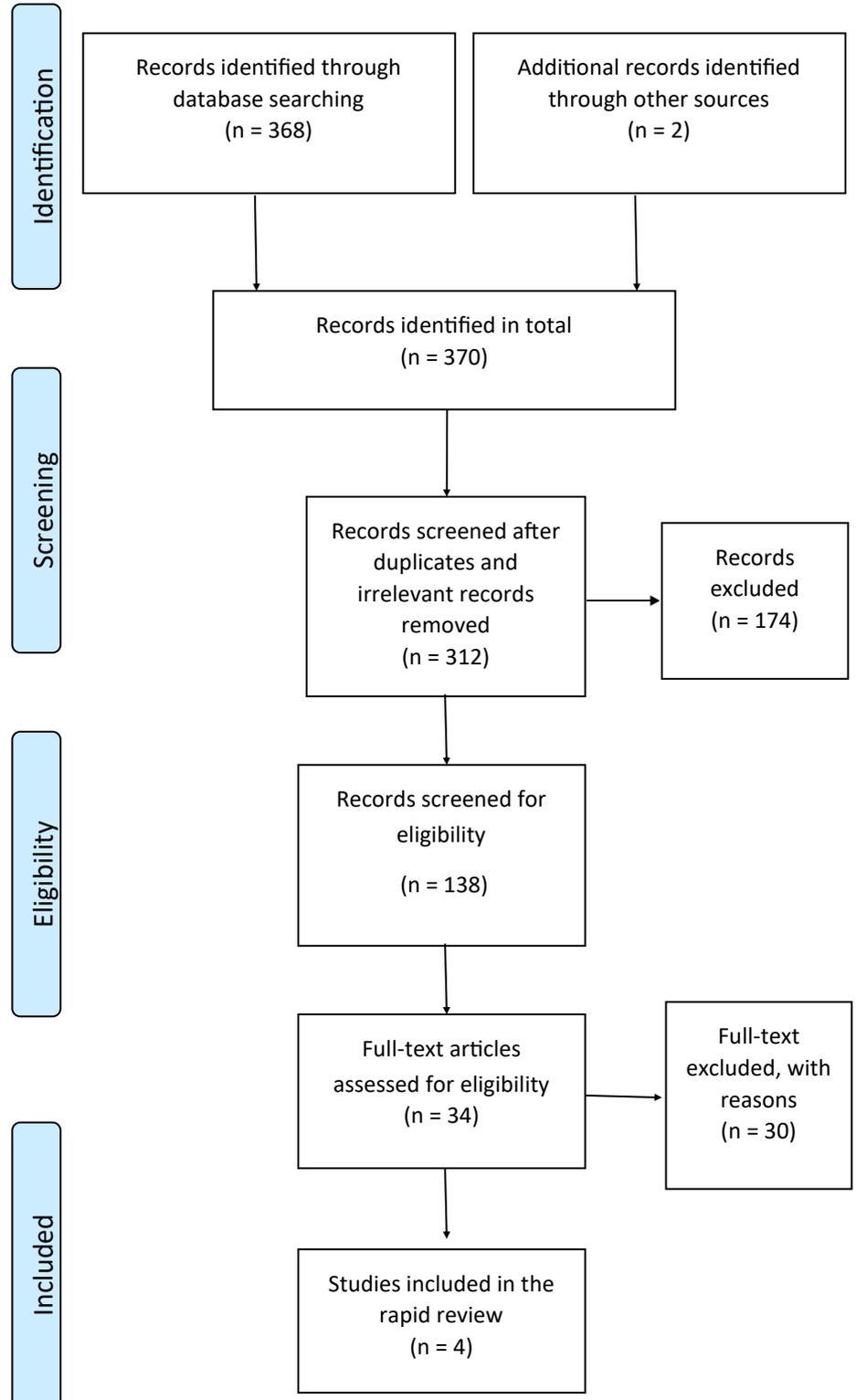## Evidence Implications:

Clinical:

There is a randomised trial evidence to support the use of a standardized algorithm (The Royal Marsden Algorithm, Andreyev et al) for managing late bowel effects of pelvic radiotherapy. Although nurse-led application of the algorithm was non-inferior to gastroenterologist application, key challenges are highlighted in relation to nurse competencies and training and the structure of clinics with direct access to medical support. A published protocol paper suggests that a study currently under way in men with prostate cancer (EAGLE Study, Taylor et al 2016) may provide further evidence on the key components which are important to the delivery of outpatient models of assessment and management of intervention. The ALERT-B tool (Taylor et al) demonstrates promise as a very short and readily applicable screening tool, with the LENT SOMA questionnaire (Barraclough et al) also appropriate for screening.

However there is a lack of evidence on interventions for urological and psycho-sexual symptoms and further guidance is required on the most appropriate tools to measure treatment outcomes across all symptom sets.

Glossary:
LENT: Late Effects Normal Tissue
SOMA: Subjective, Objective, Management, Analytic
ALERT-B: Assessment of Late Effects of RadioTherapy-Bowel
IBDQ: Inflammatory Bowel Disease Questionnaire
CONSORT: Consolidated Standards of Reporting Trials
Gy: Gray the unit of radiation administered
GI: Gastrointestinal
GSRS: Gastroenterology Symptom Rating Scale

Flow Diagram:

Identification

Records identified through database searching
(n = 368)

Additional records identified through other sources
(n = 2)

Records identified in total
(n = 370)

Screening

Records screened after duplicates and irrelevant records removed
(n = 312)

Records excluded
(n = 174)

Records screened for eligibility
(n = 138)

Eligibility

Full-text articles assessed for eligibility
(n = 34)

Full-text excluded, with reasons
(n = 30)

Included

Studies included in the rapid review
(n = 4)

Table 1: Characteristics of Included Studies

Andreyev et al 2013	Study Setting & Design – Single Cancer Centre, London, UK; Randomized Controlled Trial
Study Objective	To evaluate whether patients with chronic gastrointestinal symptoms after previous pelvic radiotherapy would achieve improved symptom control if a practitioner followed an investigative and management algorithm, and whether a nurse could apply the algorithm in such a way that outcomes were not worse than when applied by a consultant gastroenterologist: The ORBIT Trial.
Participants	Patients (aged ≥18 years) with troublesome, persisting gastrointestinal symptoms (bowel dysfunction measured by IBDQ-B score) that started during or after pelvic radiotherapy administered with curative intent. Patients were recruited at least 6 months after completion of radiotherapy. 218 were randomised out of 1608 eligible patients (271 refused, 185 not contactable, 934 no new symptoms). Full CONSORT diagram provided. Stratified by tumour site (urological, gynaecological, or gastrointestinal) and degree of bowel dysfunction
Interventions/ Comparators/ Methods	Participating patients were randomly allocated to one of three groups: 1) Usual care (a detailed self-help booklet); 2) Gastroenterologist led algorithm-based treatment; 3) Research nurse led algorithm-based treatment. The algorithm provided a step-by-step approach along a care pathway from initial identification of symptoms to long-term management. Patients were assessed at recruitment and at 6 months and 1 year after randomisation.
Outcomes	The proposed outcomes were: Primary: To detect a difference in IBDQ-B score at 6 months between standard care (booklet) and the combined intervention arms. Secondary: To compare the nurse led and gastroenterologist arms for non-inferiority for nursing intervention. To compare effects on quality of life, anxiety and depression scores, and pelvic symptom scores across arms using Rockwood Faecal Incontinence Quality of Life score, St Mark's Incontinence Score, and the LENT SOMA score at baseline, 6, 12 months.
Summary of the Study Results	Prior to study commencement a change in score of 6 or more in the IBDQ-B score was set as clinically relevant. A difference of less than 4 between the nurse and gastroenterologist arms would be considered as meaning nurse-led intervention not inferior to gastroenterologist -led intervention. Analysis was on an intention- to-treat basis. Mean improvement in IBDQ-B score at 6 months in the booklet group was not considered clinically significant (4.9, 95% CI 1.4-8.4). By contrast, a statistical and clinically significant improvement in IBDQ-B score in both the gastroenterologist led group (10.4, 95% CI 7.7-13.1) and the nurse led group (9.1, 95% CI 6.9-11.2) was seen, a pairwise mean difference versus booklet of 5.47 and 4.12 respectively. The mean difference in IBDQ-B scores between the gastroenterologist and nurse groups at 6 months was 1.36, which was much lower than the score of 4 hypothesised to indicate that nurse-led care was not worse than gastroenterologist-led care. There was no significant differences in secondary outcomes, the study was not powered to formally assess these.
Appraisal Summary	Limitations: - The majority of study patients were men, with prostate cancer the predominant diagnosis. However a subgroup analysis of this group showed almost identical outcomes to the other tumour types. - Age range was not balanced across groups. - Because of significant crossover from the booklet to the gastroenterologist group, a 12 month analysis was not possible.

Benton et al 2011	Study Setting & Design – Single Cancer Centre, London, UK; Prospective observational study
Study Objective	To describe the training, practice and clinical challenges of the nurse role in the ORBIT trial described above (Andreyev et al).
Participants	Participants in the ORBIT trial who were randomised to the nurse-led intervention arm.
Interventions/ Comparators/ Methods	As per the ORBIT trial reported above.
Outcomes	To reflect on the development of the nurse role and the inherent clinical challenges of developing a nurse-led clinic model in this context.
Summary of the Study Results	With the use of the Algorithm, median time for new appointments was 60 minutes, and follow up 40 minutes. The nurse managed patients until discharge in a median of three appointments. Twenty per cent of patients at each clinic also required doctor review. The algorithm facilitated symptom identification and initial treatment plans; second and third line treatment planning was sometimes complicated where patients' symptoms did not fit within the algorithm. Detailed, condition-specific information leaflets were highlighted as particularly important in facilitating patient discussions and education, and also in informing GPs and other healthcare professionals. Difficulties highlighted included lack of a specific training programme (a list of competencies are suggested), the need for prior physical examination by a doctor; the need for a doctor to review all letters and test results; challenges for the nurse in dealing with other cancer-related co-morbidities; challenges for the nurse in discharging patients.
Appraisal Summary	Limitations: - This is a descriptive reflection by a single nurse practitioner in a single institution. - The nurse–led clinic described occurred alongside a well established clinic run by a gastroenterologist with lengthy experience of managing pelvic radiotherapy toxicities. - The clinic described was developed within the context of a clinical trial. - There was no reporting of patient outcomes or experience in this paper.

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Barraclough et al 2012	**Study Setting & Design** – Single Cancer Centre, Manchester, UK. Prospective observational study
Study Objective	To prospectively report toxicity rates following pelvic radiotherapy for gynaecological malignancy using subjective assessments from the LENT SOMA questionnaire elicited pre-treatment, immediately post treatment, 1 year, 2 years and 3 years post treatment. Secondly, to analyse the efficacy of the questionnaire and modify on the basis of redundant items.
Participants	Patients with cervical, endometrial or vaginal cancer treated radically with external beam radiotherapy followed by intra-cavitary therapy, or adjuvantly following radical or total hysterectomy. 226 patients were prospectively recruited over a 10 year period (1998-2008). The numbers of questionnaires completed were 224, 185, 83, 66 and 57 before and immediately after, 1 year, 2 years and 3 years following treatment, respectively.
Interventions/ Comparators/ Methods	Completion of a disease site-specific questionnaire derived from the LENT SOMA scales, including 38 items from the LENT subjective scale. Questionnaires were completed before, immediately after and at 1, 2 and 3 years post treatment. Reliability of data at each collection point was assessed using Cronbach's alpha co-efficient. If more than half of a patient's answers for a subsection were missing then the patient score for that particular scale was recorded as missing. No imputation methods were used. Item scores were classified into 3 levels: no score, low or high. Maximum and mean item scores were calculated across the entire patient set for each question at each time point. Factor analysis was undertaken to identify both highly important and less informative questions using principal component analysis (PCA).
Outcomes	Analysis of patient-reported data to assess bowel function, bladder function and sexual function. Identification of both the most important and redundant questions.
Summary of the Study Results	The numbers of patients completing the questionnaire fell significantly from 224 at baseline to 185 immediately post treatment and 83, 66 and 57 at 1, 2 and 3 years respectively. Overall 126 patients withdrew from the study (patient choice, loss to follow up, too unwell). Patient reported toxicity: Bowel dysfunction peaked at 1 year: 79% described faecal urgency and 24% incontinence. Urinary symptoms took longer to develop with urinary urgency peaking at 3 years: 75% described urgency at that time point. A reluctance to answer questions on sexual function made analysis difficult to interpret. Factor analysis: Based on the PCA, 8 questions were removed as felt to be redundant. Some response items were changed and several new questions added. Overall scoring: The authors note variability in reporting LENT SOMA scores and urge care in determining symptom specific (faecal urgency, incontinence, etc) scores as overall scores alone will not adequately describe patient symptom burden.
Appraisal Summary	Limitations: - The study population was very heterogeneous: it included patients treated with or without hysterectomy before pelvic radiotherapy, and the dose varied between 40 and 45 Gy; there was also a mix of primary gynaecological tumour type. The toxicity could be expected to be higher with a combination of treatment modalities and with a higher dose of radiation. - The high withdrawal rate, and low numbers of questionnaire completions at 1, 2 and 3 years demands cautious interpretation of results. The high rates of bowel and urinary dysfunction may reflect the greater interest in continuing in the study of those who continued to be symptomatic. - There was no information on how much data was missing for individual items, or the detail of how that was handled. - There was no direct comparison in the study with other patient reported outcomes for bowel, urinary or sexual dysfunction.

Taylor et al 2016	**Study Setting & Design** – Three hospital settings across the UK; Qualitative study: cognitive and psychometric testing of a screening tool
Study Objective	To design, test and validate a simple screening tool that can effectively detect patients with ongoing gastrointestinal symptoms following pelvic radiotherapy for cancer.
Participants	Face testing using cognitive interviewing: 12 participants consisting of 6 men and 6 women recruited from oncology and gastroenterology clinics, mean age 60 (35-74yrs) who had received pelvic radiotherapy a minimum of 3 months prior to inclusion. Psychometric testing: 164 male patients participating in the EAGLE Study who had received pelvic radiotherapy for prostate cancer a minimum of 6 months prior to recruitment.
Interventions/ Comparators/ Methods	The intervention was a GI symptoms screening tool, in the form of a questionnaire. Four phases but only Phase 2 relevant to the review. Phase 1: Generation of the questionnaire screening tool (ALERT-B) Phase 2: Usability and acceptability testing through interview of patient group Phase 3: Review & refinement of the questionnaire by consensus based upon findings of phase 2 Phase 4: Psychometric validation of the tool against the Gastroenterology Symptom Rating Scale (GSRS) in patients who had received pelvic radiotherapy for prostate cancer.
Outcomes	The proposed outcomes were to identify a short screening tool that can effectively detect patients with ongoing gastrointestinal symptoms after receiving pelvic radiotherapy.
Summary of the Study Results	The final questionnaire, developed through the first three phases consisted of 3 questions. The ALERT-B screening tool was considered by participants to offer an effective way to inform healthcare professionals of their bowel symptoms to prompt further discussion. Participants felt the tool was easy to use and contained specific strengths, particularly the use of plain language and concise formatting with tick boxes enabling speedy completion of the tool. For the psychometric validation, internal consistency was measured using Cronbach's alpha coefficient and exploratory factor analysis was used for GSRS and ALERT-B to identify highly correlated items. Given the small number of items in ALERT-B a Cronbach's alpha of 0.6-0.7 was taken to reflect adequate reliability. A score of 0.61 was found. Item-scale correlations tested using Spearman's correlation coefficient were found to be high (R> 0.6). Exploratory factor analysis confirmed that ALERT-B items correlated strongly only with those GSRS items relating to bowel symptoms.
Appraisal Summary	Limitations: - The tool was designed as a screening tool only and not as an outcome measure in assessing the efficacy of interventions. - Cognitive ability of participants in the face validation study was not measured and variations may exist which may affect their ability to complete the screening tool. - The patients who responded to the invitation to participate in the study may have been a self-selected group interested to discuss their bowel symptoms. Therefore, the sample may not be fully representative of patients with late bowel effects following pelvic radiotherapy. The psychometric testing of the tool was undertaken only in male patients who had undergone pelvic radiotherapy for prostate cancer.

Included Studies:

Studies were included where the paper reported models of care which identified patients with late toxicity following pelvic radio-therapy, and effective management of that symptom burden.

1. Andreyev HJ, Benton BE, Lalji A, et al. Algorithm-based management of patients with gastrointestinal symptoms in patients after pelvic radiation treatment (ORBIT): a randomised controlled trial. Lancet. 2013;382(9910):2084-92. doi:10.1016/S0140-6736(13)61648-7

2. Barraclough LH, Routledge JA, Farnell DJ, et al. Prospective analysis of patient-reported late toxicity following pelvic radiotherapy for gynaecological cancer. Radiother Oncol. 2012;103(3):327-32. doi:10.1016/j.radonc.2012.04.018

3. Benton B, Norton C, Lindsay JO, Dolan S, Andreyev HJ. Can nurses manage gastrointestinal symptoms arising from pelvic radiation disease? Clin Oncol (R Coll Radiol). 2011;23(8):538-51. doi:10.1016/j.clon.2011.03.006

4. Taylor S, Byrne A, Adams R, et al. The Three-item ALERT-B Questionnaire Provides a Validated Screening Tool to Detect Chronic Gastrointestinal Symptoms after Pelvic Radiotherapy in Cancer Survivors. Clin Oncol (R Coll Radiol). 2016;28(10):e139-47. doi:10.1016/j.clon.2016.06.004

References to ongoing study:

Taylor S, et al. Improving the well-being of men by Evaluating and Addressing the Gastrointestinal Late Effects (EAGLE) of radical treatment for prostate cancer: study protocol for a mixed-method implementation project. BMJ Open 6.10 (2016): e011773.

Excluded Studies:

A number of studies have been excluded due to various reasons including the following: Description regards prevalence of late effects, and studies with no direct relevance to clinic process and outcomes.

Additional materials available upon request:

- Critical appraisal / data extraction forms
- Search strategies
- List of excluded studies

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