Meta-analysis of outcomes following aneurysm repair in patients with synchronous intra-abdominal malignancy

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What this study adds to the existing literature and how it will influence future clinical practice

The aim of this study was to determine outcomes in patients undergoing abdominal aortic aneurysm (AAA) repair [endovascular (EVAR) or open] who have a synchronous malignancy. Synchronous intra-abdominal cancer is relatively common in patients undergoing AAA-repair and surgeons are faced with the dilemmas of what type of repair to offer and in what sequence. Our findings support that EVAR is superior regarding short-term mortality. Both EVAR and OAR were associated with significant short-term morbidity, which merits careful planning and close follow-up in this patient group. Future studies should look into the optimal timing of AAA-repair, for which limited data exist.

ABSTRACT

Objectives: The management of concomitant intra-abdominal malignancy (IAM) and abdominal aortic aneurysm (AAA) remains a challenge, even though malignancy is common in this elderly population. We aimed to investigate outcomes in patients undergoing open (OAR) or endovascular AAA repair (EVAR) that have a concomitant malignancy through a systematic-review and meta-analysis.

Methods: A systematic literature-review was performed (Medline and EMBASE databases) to identify all series reporting outcomes of AAA-repair (OAR or EVAR) in patients with concomitant IAM. Meta-analysis was applied to assess mortality and major-morbidity at 30-days and long-term.

Results: The literature review identified 36 series (543 patients) and the majority (18 series) reported on patients with colorectal-malignancy and AAA. Mean weighted-mortality for OAR at 30-days was 11% [95% Confidence Interval (CI): 6.6% to 17.9%]; none of the EVAR patients died peri-operatively. The weighted 30-day major complication-rate for EVAR was 20.4% (10.0% to 37.4%) and for OAR it was 15.4% (7.0% to 30.8%). Most patients had their AAA and malignancy treated non-simultaneously (56.6%, 95% CI: 42.1% to 70.1%). In the EVAR cohort 3 patients (4.6%) died at last follow up (range 24 to 64 months). In the OAR cohort 23 (10.6%) had died at last follow up (range from 4 to 73 months).

Conclusion*:* In this meta-analysis, OAR was associated with significant peri-operative mortality in patients with an IAM. EVAR should be the first line modality of AAA repair. The majority of patients were not treated simultaneously for the two pathologies, but further investigation is necessary to define the optimal timing for each procedure and malignancy.

Keywords: abdominal aortic aneurysm, cancer, malignancy, outcomes

Introduction

The management of concomitant abdominal aortic aneurysms (AAA) and intra-abdominal malignancy (IAM) is challenging. The introduction of endovascular AAA repair (EVAR), which has favourable early and medium-term outcomes(1, 2), has further complicated decision-making in this context. Certain patients may not require surgical resection, but in those that do, the dilemma is whether to treat the AAA first, which risks delaying the treatment of the cancer, or to treat the cancer first with the potential risk of AAA-rupture and death. A third option is to treat both pathologies simultaneously, especially if the patient is fit enough to undergo a prolonged procedure. However, simultaneous AAA and cancer procedures may be associated with increased risk of graft infection, especially within the context of synchronous gastrointestinal surgery and open aneurysm repair (OAR). Furthermore, cancer resection is fraught with an increased risk of bleeding as anticoagulation is necessary for aneurysm surgery (OAR or EVAR). This increased risk of bleeding may be offset by an increased hypercoagulable state often associated with malignancy (3), however this may compromise the subsequent post-operative graft patency and peripheral thrombo-embolic complications following OAR or EVAR. Thus the clinical problem is complex.

Randomised-trials have shown short-term superiority of EVAR over OAR (1, 2, 4) and the majority of patients have anatomy suitable for EVAR(5, 6). In the current minimally invasive era there is a need to determine the effect of malignancy on outcomes following EVAR and the risks of EVAR in patients with concomitant IAM.

Following the above, the aim of this study is to assess mortality and morbidity in patients with a synchronous AAA and an IAM, through a systematic literature-review and meta-analysis.

METHODS

Search Strategy

The Medline (1950 to present), EMBASE (1980 to present), Cochrane Library and Google Scholar (Timeframe = "Anytime") databases were interrogated (date of electronic search: 15th July 2015) to identify all relevant manuscripts reporting outcomes after AAA repair in patients with a concomitant malignancy. The search was limited to studies in human. Various combinations of MeSH terms, phrases and free text were used to ensure all relevant articles were identified. The search terms were: Cancer, neoplasia, tumo(u)r, abdominal aortic aneurysm. Search terms were combined with the use of Boolean operators (AND, OR, NOT). Titles and Abstracts of all publications identified through the search strategy were screened by AS, OA, and RK independently and consensus regarding inclusion of each manuscript in the analysis was reached following discussion with the senior authors (AS, RDS, MJB). At this stage, once all relevant publications identified through the online search had been obtained, the references of all manuscripts were also manually searched (by AS and RK) to identify potential publications that had been missed. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidance was adhered to at all stages(7, 8). Authors were contacted twice to obtain missing data; manuscripts not reporting at least peri-operative mortality were not included.

Inclusion Criteria

Any papers that reported (and where data could be extracted) patient outcomes on intra-abdominal visceral cancer in the context of AAA were included.

Exclusion Criteria

Articles that contained only a single case (i.e. case report) and conference proceedings were excluded. The authors of papers with missing information were contacted to obtain relevant missing data and if no operative outcomes could be obtained, these publications were excluded.

Study Selection

Two independent reviewers (RK, OA) selected the appropriate studies for both inclusion and exclusion criteria. Discrepancy between reviewers was resolved by a third independent author, AS. No specific quality criteria were applied when excluding articles, given that no prospective randomized articles were identified and all relevant publications consisted of case-series, mostly of retrospective nature. The Newcastle–Ottawa scale (9)was used to assess study-quality by examining patient selection methods, comparability of groups and assessment of outcome. None of the series included in the eventual analysis achieved a rating of more than 4 stars.

Definitions

Abdominal aortic aneurysm was defined as aortic diameter exceeding 3.0cm on cross-sectional imaging. Complications and other patient and procedural characteristics were defined using the reporting criteria by Ahn and Chaikof et al for OAR and EVAR (10, 11).

Outcome definitions

The primary outcome measure was 30-day mortality. Further outcomes extracted from the articles included aneurysm-related complications (graft limb occlusions, re-interventions, endoleaks and sac expansions) during the peri-operative period and long-term follow-up, overall patient survival and major complications; all events are reported using the aforementioned reporting criteria(10, 11).

Statistical analysis

Analyses were performed using the R Package for Windows (version 3.0). Continuous variables of interest are reported using mean values and standard deviation (SD) or median values and range, for parametric and non-parametric data respectively. Random or fixed effects meta-analysis was performed using the proportions of patients who experience an event (inpatient or 30-day mortality) as outcome data, as necessary, based on between-study heterogeneity. The latter was assessed using the I^2 statistic, which describes the percentage of total variation across studies that arises due to heterogeneity rather than chance or random error. A value greater than 50% was considered to reflect significant

heterogeneity owing to real differences in study populations, protocols, interventions and outcomes for the purposes of this study and hence a random effects model was used in this case. A p value level <0.05 was considered statistically significant. The Newcastle–Ottawa scale (9)was used to assess study quality.

RESULTS

Search Results

The initial electronic search identified a total of 658 potential journal articles and after removal of 27 duplicates, a total of 631 unique article titles and abstracts were reviewed, as described above. From this, 258 were deemed to be suitable for full-text review. Following that, we identified 36 case-series (analysed in 29 separate publications) meeting our inclusion and exclusion criteria (Figure 1 – PRISMA chart)(12-41). Regarding exclusion of non-intra-abdominal malignancies identified in the literature, 2 case-reports reported on outcomes after EVAR on patients with lymphoma (excluded) and 1 series reported on lymphoma incidence after EVAR. A further 4 case reports reporting on patients undergoing EVAR with concomitant lung cancer we also excluded. All series included in the literature synthesis were retrospective reports; no randomized trials or prospective cohort-studies were identified. All articles included in the synthesis had a 3 or 4 star rating based on the Newcastle-Ottawa scale, hence no study-quality related exclusion criteria where applied. Articles included in the analysis were published between 1989 and 2015; only 1 article was published prior to the introduction of EVAR in 1991 and 5 prior to 2000. None of the articles described outcomes pertaining to repair of type IV, supra-renal or inflammatory/mycotic aneurysms.

These series reported outcomes in patients undergoing operative intervention of AAA within the context of IAM: 18 colorectal, 9 urological, 3 gastric and 1 pancreatic malignancy. Five series described outcomes in a variety of mixed cancers. This review focuses on elective AAA repairs; overall 10 emergency AAA repairs were described but these were excluded from the subsequent data synthesis.

Four of these patients experience a rupture whilst awaiting AAA treatment after cancer surgery; no rupture occurred whilst awaiting cancer surgery.

A total of 8 series reported solely EVAR outcomes, whilst 16 reported on OAR and the remaining 12 series reported on both OAR and EVAR. Tables 1, 2 and 3 describe study characteristics and reported outcomes.

Mortality

The overall weighted 30-day all-cause mortality for the entire 36 series (including both EVAR and OAR) was 9.6% [6.7% to 13.2%, 95% Confidence Interval (CI); I^2: 0, p=0.98]. For the studies that reported mortality separately for EVAR and OAR, the overall weighted 30-day mortality for OAR was 11% (6.6% to 17.9%, I^2: 0, p=0.84); none of the patients in the EVAR series (7 publications reporting on 37 patients) had died at 30 days (Tables 1 to 3 and Figure 2). For the series reporting only colorectal malignancies, the cumulative mortality at 30 days was 2.4% (1.2% to 5.5%).

Morbidity

The overall 30-day major complication-rate was 17.4% (11.4% to 25.4%, I^2: 56.9%, p<0.001). Type II endoleaks and events that did not require intervention or hospital admission were not considered as major complications, as per Chaikof et al(10). The equivalent overall weighted 30-day major complication-rate for EVAR was 20.4% (10% to 37.4%, I^2: 0, p=0.58) and 15.4% for OAR (7% to 30.8%, I^2: 0, p=0.63). The proportion of patients having their cancer and AAA treated simultaneously was 42% (30% to 52.3%) and non-simultaneously was 56.6% (42.1% to 70.1%). There was great variability regarding the timing of treatment in the non-simultaneous groups (cancer or AAA first) amongst the series (Tables 1 to 3). As a result, given the lack of individual patient data, we could not perform a meaningful analysis regarding the association between timing of repair (cancer or AAA first) and subsequent outcomes.

Long-term Results

Long-term outcomes were reported in a non-uniform manner across the 36 series and none reported the precise number of patients adhering to follow-up at specific time-points, prohibiting meta-analysis for long-term events (mortality and morbidity). Seven case series (5 publications) reported cancer recurrence data during follow-up on 31 patients who underwent EVAR. Of these 31 patients there were no recurrences of cancer at the last known follow-up (mean number of months ranged from 24 to 64 months). Twelve individual series reported recurrence of cancer data within the context of OAR for a total of 81 OAR patients. Ten of these 81 patients (12.3%) were found to have recurrence of their primary cancer within the date of the last known follow up (mean number of months ranged from 17.5 to 73 months). Data from 11 series (9 papers) allowed identification of 'any cause' mortality rates to be determined for EVAR patients (total n=65) whilst 17 OAR series were identified (total n=217 patients). "Any cause mortality" was defined to have occurred outside of the peri-operative, 30 day period, as these may be reasonably attributable to operative intervention(s) and/or short-term complications. In the EVAR cohort 3 patients (4.6%) had died at last known follow up (mean number of months ranged from 24 to 64 months). In the OAR cohort 23 (10.6%) had died at last known follow up (mean number of months ranged from 4 to 73 months).

Discussion

In this study we aimed to apply meta-analysis to a literature review of 36 case series pertaining to operative intervention in AAA within the context of concurrent intra-abdominal malignancy. We aimed to assess whether OAR or EVAR was favourable within the context of intervention for cancer be it: prior to, simultaneously or after surgical intervention for cancer. We looked at outcomes primarily with respect to 30 day complications (mortality, morbidity) as long-term data were not uniformly reported to allow meta-analysis at specific time-point. However, in the longer term, we did determine mortality at last known follow up and cancer recurrence for a subset of studies with such available data. Overall, this study suggests that EVAR has favourable short-term mortality rates compared to OAR in the

context of malignancy, but morbidity is high (compared to historical data for malignancy-free patients) after both EVAR and OAR, which merits for closer follow-up.

The present meta-analysis is of pertinence because increasingly 'Cancer and Neoplasms' as a disease entity represent the leading causes of death in England and Wales(42). The World Health Organisation forecasts deaths from cancer to continue to increase globally (WHO)(42). Arguably, therefore, a concurrent malignancy in patients presenting with an AAA will be an increasingly common issue that vascular surgeons will have to face in the future, especially given that minimally invasive methods now allow treatment of pathologies with relative safety in older and frailer individuals. As a result, it is important to be aware of which treatment strategy is optimal and associated short and long-term outcomes.

Earlier studies investigating outcomes in patients with cancer and AAA largely focused on complications following OAR and aimed to determine the best management approach for those with both pathologies. Most studies advocated sequential tumour resection before or after OAR whilst a minority recommended simultaneous open surgery. The latter does bear the risks of graft infection and bleeding due to anticoagulation (heparin) during the AAA procedure. In the current endovascular era, however, these recommendations are no longer applicable, given the minimally invasive nature of EVAR (does not require a laparotomy) and the fact that modern devices and contemporary techniques such as fEVAR have widened the anatomical spectrum of EVAR(43). However, conversely, the pro-coagulable state associated with the presence of malignancy is an important consideration and confers yet another co-morbid factor that may adversely impact on limb patency and increased post-operative ischaemia secondary to thrombo-embolic events, such as limb occlusion, after EVAR.

In one of the very few publications directly comparing EVAR and OAR in the context of malignancy, Porcellini et al (38) compared the impact of treating patients with cancer and AAA with either OAR or EVAR and found that EVAR was associated with a shorter length of stay, fewer post-operative complications and better survival outcomes at both 1- and 2-years. As a result, they recommend that EVAR followed by cancer resection should be considered as the preferred option in patients with

morphologically suitable aneurysms. Unfortunately, further comparative data in the literature for this population are insufficient to allow meaningful meta-analysis with cumulative odds/hazard ratios to be undertaken. We therefore set out to combine literature reports on EVAR and OAR separately, in patients with malignancy. Morbidity rates in our meta-analysis, were relatively high following both OAR and EVAR, in comparison to AAA repair per se in the absence of IAM [20.4% for EVAR at 30 days (10% to 37.4%) and 15.4% for OAR at 30 days (7% to 30.8%)]. However, there were no peri-operative deaths following EVAR. Interestingly, the OAR in this meta-analysis was also associated with high long term 'any cause' mortality; 10.6% at last follow up compared with 4.6% in the EVAR cohort. Direct comparisons at specific time-points were not possible for these long term outcomes due to lack of patient specific data from the reports.

The most prevalent cancer types in those undergoing EVAR in the literature were colorectal and urological malignancies and this is similar to the prevalence reported by Porcellini et al (38). Most of the previous studies in this area have focused on colorectal malignancies despite the fact that other gastrointestinal and urological malignant resections also require intra-abdominal intervention and therefore pose comparable risks in terms of post-operative AAA rupture. Therefore, our rationale was to include all types of IAM in our systematic review. We are not aware of another publication endeavouring to pool data for all patients with IAM and AAA. The majority of series did focus on colorectal malignancy in our literature synthesis, but we identified another 17 series which reported on other types of malignancy. We have not included other types of malignancy (such as lymphoma, lung cancer) due to the fact that there are only scarce reports in the literature in patients with such a malignancy and a synchronous AAA. Also, these do not require resection of an intra-abdominal tumour in order to be treated curatively.

A number of biological mechanisms exist by which cancer could influence outcomes in patients with AAA, which could explain the high-rate of morbidity observed in this study. Angiogenesis is defined as the de novo formation of new blood vessels. Both cancer and AAA share angiogenesis as a common feature in their pathophysiology(44), with angiogenesis being important for tumour growth and metastasis as well as AAA growth and rupture(45). Since EVAR does not remove the aneurysm sac

from the body, it is possible that sac regression may fail to occur after EVAR, as a result of release of pro-angiogenic factors by malignant tissues, with a resultant increased propensity towards endoleaks, sac expansion and even rupture. Other biological pathways that may be affected by concomitant malignancy are those regulating thrombosis and inflammation. The ability of cancer to induce a hypercoagulable state is well known (3) and this may have implications if such a state increases the rate of graft limb occlusions. Additionally, patients with cancer are often prescribed prolonged courses of non-steroidal anti-inflammatory analgesia or steroids for intracranial pressure symptoms, both of which have the potential to influence AAA growth. Inflammation is a key component in AAA pathophysiology. It is therefore important to offer closer follow-up to this patient group following their intervention to treat the AAA.

The optimal timing of AAA repair prior to cancer surgery, during or following remains uncertain. Certain malignancies, such as an isolated renal carcinoma, may offer themselves to resection through a retro-peritoneal approach with minimal soiling whilst performing an OAR. However, this may not be the case for a pelvic rectal cancer or a right sided colonic neoplasm. The necessity for bowel resection and possible inoculation of the stent graft material would have the potential for catastrophic post-operative consequences. Such patients may benefit from EVAR to treat the AAA and the present meta-analysis does suggest that EVAR is a safe technique in this patient group despite a possible hyper-coagulable state(3); however, timing of interventions remains an unsolved issue. Further investigation is necessary to define the best-timing for each procedure; meaningful analyses were not possible in our report due to lack of data in the series identified. This may be further investigated in a well-designed prospective observational study.

Limitations

The principal limitation of this study is the retrospective nature of the articles included in the data synthesis, evidenced by the low star rating (3 or 4 stars for all manuscripts included) that the publications achieved using the Newcastle-Ottawa scale. Individual level patient data were largely not available, apart from the few patients who had an emergency repair, outcomes for which were described

291 in some detail (these were excluded from the meta-analysis to remove bias). Hence, we could not
292 perform meaningful data synthesis regarding timing of aneurysm repair with respect to cancer
293 intervention and therefore the subsequent outcomes. Furthermore, we cannot comment on the risk-
294 profile of patients who should be offered AAA repair if they do have a malignancy, given that data
295 regarding the fate of patients managed conservatively is lacking. Another interesting parameter is
296 reporting bias; especially for the EVAR patients, where no deaths were seen within 30 days, there may
297 have been some under-reporting of bad outcomes. Finally, some of the EVAR series in the meta-
298 analysis have utilised early generation EVAR devices, which are known to be associated with inferior
299 outcomes.

300 In conclusion early morbidity rates were significant in our meta-analysis but EVAR is superior
301 regarding short-term mortality. A well-designed observational study is required to define the best timing
302 for each procedure in the context of malignancy.

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304 **Figure legends**

305 **Figure 1:** PRISMA flow chart for meta-analysis.

306 **Figure 2:** Forest plot describing mortality at 30-days after open aneurysm repair.

307 **Figure 3:** Major complication rates following endovascular aneurysm repair.

308 **Figure 4:** Major complication rates following open aneurysm repair.

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