

The impact of immediate breast reconstruction on the time to delivery of adjuvant therapy: The iBRA-2 Study

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ABSTRACT

Background

Immediate breast reconstruction (IBR) is routinely offered to improve quality-of-life for women requiring mastectomy, but there are concerns that more complex surgery may delay adjuvant oncological treatments and compromise long-term outcomes. High-quality evidence is lacking. The iBRA-2 study aimed to investigate the impact of IBR on time to adjuvant therapy.

Methods

Consecutive women undergoing mastectomy+/-IBR for breast cancer July-December,2016 were included. Patient demographics, operative, oncological, and complication data were collected. Time from last definitive cancer surgery to first adjuvant treatment for patients undergoing mastectomy+/-IBR were compared and risk-factors associated with delays explored.

Results

2,540 patients were recruited from 76 centres; 1,008 (39.7%) underwent IBR (implant-only [n=675,26.6%]; pedicled-flaps [n=105,4.1%] and free-flaps [n=228,8.9%]). Complications requiring readmission or reoperation were significantly more common in patients undergoing IBR than those receiving mastectomy. Adjuvant chemotherapy or radiotherapy was required by 1,235(48.6%) patients. No clinically-significant differences were seen in time to adjuvant therapy between patient groups but major complications irrespective of surgery received were significantly associated with treatment delays.

Conclusion

IBR does not result in clinically-significant delays to adjuvant therapy but post-operative complications are associated with treatment delays. Strategies to minimize complications including careful patient selection are required to improve outcomes for patients.

1 BACKGROUND

2 Breast cancer is the most common female cancer worldwide with 1.7 million new cases diagnosed each
3 year ¹. Despite improvements in treatment, however, mastectomy remains the primary surgical
4 treatment for almost 40% of women ^{2,3} and immediate breast reconstruction (IBR) is offered with the
5 aim of improving quality of life ⁴.

6 Although psychosocial outcomes are an important consideration when planning treatment, oncological
7 safety remains paramount. Breast reconstruction is associated with more complications than simple
8 mastectomy ⁵ and concerns have been raised that the increased complication rate may lead to the delay
9 or omission of adjuvant chemotherapy or radiotherapy ⁶ which may compromise oncological outcomes.

10 The clinical significance of short delays is unclear, but two recent large population-based studies have
11 shown that patients experiencing delays of more than 90 days in the delivery of chemotherapy
12 experienced worse overall and cancer-specific survival ^{7,8}. Furthermore, a recent meta-analysis
13 suggests a 15% decrease in overall survival for every four week delay in the delivery of adjuvant
14 chemotherapy ⁹. Delays to radiotherapy have similarly adverse effects but the time-frames are less
15 well-established. A meta-analysis including 21 retrospective breast cancer studies suggested an
16 increased risk of loco-regional recurrence if radiotherapy was delayed by more than eight weeks
17 following surgery¹⁰ but other large cohort studies have demonstrated no deleterious effects with delays
18 of up to 20 weeks ¹¹.

19 Evidence regarding the impact of IBR on the delivery of adjuvant therapy, however, is inconsistent ⁶. A
20 recent systematic review ⁶ failed to demonstrate a clinically-significant delay in the initiation of
21 chemotherapy but included 14 mainly single-centre studies with significant heterogeneity and these
22 results cannot be relied upon. Two large population-based studies, however have recently reported
23 delays to the start of chemotherapy in the patients undergoing IBR. One study did not differentiate
24 between types of breast reconstruction ⁷ and the second used patients undergoing breast conserving
25 surgery as a control group and demonstrated delays in patients undergoing mastectomy without
26 reconstruction as well as those undergoing immediate autologous reconstruction procedures ⁸ making
27 these findings difficult to interpret.

28 High-quality evidence regarding the impact of IBR on the delivery of adjuvant therapy compared with
29 mastectomy alone is therefore lacking. Randomised trials (RCTs) provide the best evidence of treatment
30 effect but are inappropriate in this context. A large-scale prospective cohort study is therefore required

to generate high-quality data to allow patients and surgeons to make more informed decisions about potential treatment options. The trainee research collaborative model has recently emerged as a time and cost-effective method for delivering large-scale prospective studies in reconstructive breast surgery¹². This network of breast and plastic surgeons was utilized to deliver the iBRA-2 study to determine the impact of IBR on the delivery of adjuvant treatment¹³.

METHODS

Study design and participants

A prospective multi-centre cohort study was used to determine whether IBR influenced time to delivery of adjuvant therapy compared to mastectomy alone.

All breast or plastic surgical units performing mastectomy with or without IBR were invited to participate through the UK Trainee Collaborative Research Network (the Mammary Fold Academic and Research Collaborative and the Reconstructive Surgery Trials Network) and the UK professional associations (Association of Breast Surgery [ABS] and the British Association of Plastic Reconstructive and Aesthetic Surgeons [BAPRAS]).

Consecutive women aged 18 or over undergoing mastectomy with or without IBR using any technique for invasive or pre-invasive (ductal carcinoma in situ, DCIS) breast cancer with curative intent at participating centres between 1st July and 31st December 2016 were recruited to the study. Excluded were patients undergoing risk-reducing surgery (without a therapeutic mastectomy for breast cancer), partial mastectomy including wide local excision with volume replacement (latissimus dorsi mini-flaps; lateral intercostal perforator (LICAP) or thoracodorsal artery perforator (TDAP) flaps) or displacement techniques (therapeutic mammoplasty), and those with distant metastatic disease.

This study was classified as service evaluation by the UK National Health Service Research Authority Decision Tool (<http://www.hra-decisiontools.org.uk/research/index.html>) so individual patient consent was not required. Each participating centre registered the study and obtained local clinical governance approvals prior to commencing patient recruitment. The study protocol was published in 2016¹³.

Procedures

Patients were identified prospectively from clinics, multidisciplinary team (MDT) meetings and operating theatre lists. Simple demographic, co-morbidity, operative, and oncology data were collected for each

participant. Decisions regarding the recommendation for adjuvant treatment were identified from the post-operative MDT meeting.

For patients in whom adjuvant therapy was recommended, data were collected on whether the offer was accepted and in patients electing to receive adjuvant therapy, date of the first treatment was recorded.

Data regarding post-operative complications were collected prospectively until the patient commenced adjuvant therapy or it was decided that adjuvant therapy would be omitted due to post-operative complications. Preliminary work suggested that adjuvant therapy was unlikely to commence earlier than six weeks post-operatively. Data collection in patients not requiring adjuvant treatment therefore continued from the last definitive cancer surgery until six weeks following surgery either by clinical assessment or note-review in those not attending for follow-up.

The REDCap electronic data-capture system ¹⁴ (<http://www.projectredcap.org/>) was used data collection.

The study processes were piloted over a four-week period to ensure the feasibility of the study and to refine the case report forms prior to commencing national recruitment.

For the purposes of the analysis, patients were categorised into four groups according to the most complex procedure received as: i) mastectomy only without reconstruction; ii) mastectomy and IBR with implant-only techniques; iii) mastectomy and IBR with pedicled flaps and iv) mastectomy and IBR with free-flap techniques. Implant-based procedures included any reconstruction in which only expanders/implants were used to reconstruct the breast. This included one or two-stage procedures with or without biological (e.g. acellular dermal matrix) or synthetic (e.g titanium-coated polypropylene) mesh irrespective of whether the implant/expander was placed in a pre or subpectoral position. Pedicled-flap procedures included any pedicled-flap used to reconstruct the breast with or without an implant/expander and included latissimus dorsi (LD) and transverse rectus abdominus myocutaneous (TRAM) flaps. Free-flap procedures included any technique in which a microvascular free-flap was used for IBR and included deep inferior epigastric perforator (DIEP), superficial inferior epigastric perforator (SIEA), superior and inferior gluteal artery perforator (SGAP and IGAP), and transverse upper gracilis, (TUG) procedures.

1 Outcome measures

2 The primary outcome was time in days from last definitive cancer surgery to the first adjuvant treatment.
 3 The last definitive cancer surgery included any additional procedures recommended by the MDT for
 4 oncological reasons (e.g. axillary clearance) but did not include any surgery for post-operative
 5 complications (e.g. debridement of skin-flap necrosis). First adjuvant therapy was defined as the first
 6 dose of chemotherapy or the first fraction of radiotherapy. Time to endocrine therapy was not included.
 7 In patients for whom more than one modality of adjuvant treatment was recommended, only the start
 8 date for the first adjuvant therapy was recorded. Significant treatment delays to i) chemotherapy and ii)
 9 radiotherapy were defined based on the best available evidence ^{7,8,10} as delays of greater than 90 days
 10 for chemotherapy ^{7,8} and greater than eight weeks for radiotherapy ¹⁰.

11 Secondary outcomes included post-operative complications, readmission to hospital following discharge
 12 and unplanned re-operation for complications within 6 weeks of the last definitive cancer surgery or prior
 13 to the start of adjuvant therapy. All complications were defined a priori. Major complications were defined
 14 as any complication requiring readmission or re-operation. Minor complications were defined as those
 15 managed conservatively ¹³.

16 Quality assurance

17 For quality assurance (QA) purposes, the principal investigator at each participating site was asked to
 18 independently validate 5-10% of the submitted data for each unit and to check complete case
 19 ascertainment. If concordance between the data entered on REDCap and that independently-validated
 20 was <90%, the unit's data were excluded from the analysis consistent with the QA procedure used in
 21 other collaborative projects ¹³.

22 Statistical analysis

23 Descriptive summary statistics were calculated for each variable for the cohort overall and split by
 24 operative procedure. Categorical data were summarised by counts and percentages. Continuous data
 25 was summarised by median, interquartile range (IQR) and range. Procedure groups were compared
 26 using appropriate non-parametric statistics. Complications and oncological outcomes were summarised
 27 by procedure and by patient.

28 Univariable and multivariable logistic regression analysis was used to explore clinico-pathological
 29 variables hypothesised to be associated with the development of i) any complication and ii) major

complications, as these were considered most likely to impact on time to adjuvant therapy. Variables of interest were defined a priori based on the literature and expert opinion and included patient and procedure-related variables, namely age, smoking, body mass index (BMI), diabetes, ischaemic heart disease (IHD), other co-morbidities, previous surgery and/or radiotherapy to the ipsilateral breast; neoadjuvant chemotherapy (NAC), American Society of Anesthesiologists (ASA) grade, unilateral vs bilateral surgery, type of axillary surgery (none, sentinel node biopsy [SNB] or axillary node clearance [ANC]), and procedure type (mastectomy, implant-based, pedicled, or free-flap reconstruction).

Time from surgery to first adjuvant therapy was calculated for all patients and for those undergoing i) chemotherapy and ii) radiotherapy as their first adjuvant treatment separately in each procedure group, with adjuvant therapy as the event. This analysis was repeated stratifying by whether the patient had no, minor, or major complications. Kaplan-Meier analyses, univariable and multivariable Cox survival models of time to first adjuvant therapy and time to i) chemotherapy and ii) radiotherapy separately split by procedure type were created, including patient age, BMI, diabetes, IHD, other comorbidities, smoking, , ASA grade, unilateral vs bilateral surgery, procedure type, and the presence of complications (none, minor or major) as variables of interest, clustered by centre. The Kaplan-Meier graphs of time to adjuvant therapy were curtailed at 150 days, when only 10 patients remain in follow-up, to better focus on the majority of patients.

STATA 15 (STATA, Inc., Texas) was used for all analyses.

RESULTS

In total, 2,652 patients were recruited to the study from 76 centres across the UK (n=66), Europe (n=9) and North Africa (n=1). Of these, 112 (4.4%) were excluded; 19 (0.7%) had surgery outside of the study period; 55 (2.1%) had risk-reducing surgery only; 6 (0.2%) did not undergo a mastectomy and 24 (0.9%) had incorrect or important missing data (e.g. operation date or procedure type). Eight (0.3%) patients had 'other' forms of reconstruction. These could not be appropriately categorised so were excluded. 2,540 patients were therefore included in the analysis. Of these, 1,008 (39.7%) underwent IBR with implant-based (n=675), pedicled-flaps (n=105) or free-flap (n=228) techniques.

Patient demographics

Patient demographics are summarised in table 1. Women undergoing IBR were younger and had fewer co-morbidities than patients undergoing mastectomy only. More patients undergoing IBR received NAC

than those undergoing simple mastectomy and patients undergoing IBR were more likely to have undergone an up-front SNB prior to their reconstruction, particularly if they were undergoing tissue-based procedures. Bilateral surgery for risk-reduction or symmetry was more common in patients undergoing implant-based or free-flap reconstruction (table 1).

Post-operative complications

The 2,540 patients underwent 2,732 procedures including 773 implant-based reconstructions (157 subpectoral expanders; 410 subpectoral reconstructions with biological or synthetic mesh; 105 dermal-sling procedures and 98 prepectoral reconstructions), 106 pedicled-flaps (62 autologous LD, 39 LD with implant, 2 pedicled TRAM and 2 other), and 247 free-flap procedures (219 DIEPs, 16 free TRAMs, 4 SIEA, 7 TUG flaps and 1 other). Details of complications by procedure are summarised in supplementary table 1.

Overall, 929 (36.6%) of patients in the study experienced at least one post-operative complication (table 2). Univariable analysis identified age, BMI, IHD, diabetes, having other comorbidities, smoking, ASA grade, and undergoing an ANC but not IBR as risk factors associated with developing a post-operative complication (table 2). Age, BMI, having other co-morbidities, smoking, and undergoing an ANC remained strongly associated with post-operative complications in the multivariable model, whilst undergoing bilateral surgery and free-flap reconstruction were also identified as independent risk factors for complications in the multivariable analysis.

Major complications which required readmission to hospital or further surgery (table 2) were experienced by 221 (8.7%) of patients. Implant-based and free-flap reconstruction, age, BMI, smoking, and bilateral surgery were associated with major complications in the univariable analysis. All of these variables except for age, remained strongly associated with major complications in the multivariable model but implant-based (adjusted Odds Ratio [aOR] 4.34, 95% Confidence Interval [CI] 2.35-7.99) and free-flap reconstruction (aOR 4.88, 95% CI 2.63-9.04) were the strongest predictors for major complications in this analysis (table 2).

Adjuvant treatment recommendations and time to adjuvant therapy

Table 3 summarises the post-operative pathology for the 2,607 mastectomies performed for oncological indications. IBR was more likely to be performed following mastectomy for extensive DCIS or multifocal

disease and in node-negative patients than simple mastectomy resulting in fewer patients in the IBR group requiring adjuvant chemotherapy or radiotherapy.

Overall 1,235 (48.6%) patients were offered and accepted adjuvant treatment (table 4). Time to adjuvant treatment differed between the groups, with those undergoing free-flap procedures having longer time to adjuvant therapy than those undergoing mastectomy only, adjusted hazard ratio (aHR) 0.84 (95% CI 0.71-0.99), (table 5, figure 1a). The absolute differences between the median time to adjuvant treatment across the groups, however, were small; 52 (IQR 41-6) days for mastectomy only versus 57 (IQR 46-72) days for free-flap reconstruction (table 5). The development of complications (figure 1b) and obesity were also associated with longer time to adjuvant therapy (table 5). Median time to first chemotherapy was 47 days, (IQR 37-59). There were no significant differences in median time to chemotherapy or in the proportions of patients experiencing delays of greater than 90 days between the treatment groups (table 4) but free-flap reconstruction (aHR 0.79, [95% CI 0.65-0.96]), major complications (aHR 0.72, [95% CI 0.54-0.94]) and obesity (aHR 0.75, [95% CI 0.57-0.99]) were associated with having longer time to chemotherapy in the multivariable model (supplementary table 2). Median time to first fraction of radiotherapy was 60 days (IQR 48-73) with no differences in either the median time to radiotherapy or the proportion of patients experiencing significant treatment delays, defined as greater than 8 weeks, between procedure types (table 4). Major complications (aHR 0.70, [95% CI 0.53-0.93]) and smoking (aHR 0.73, [95% CI 0.57-0.94]) were associated with longer time to adjuvant radiotherapy in the multivariable model with older patients and those who had received neoadjuvant chemotherapy proceeding to radiotherapy more rapidly than other patient groups (supplementary table 3).

Time to first adjuvant therapy ($p<0.001$), time to chemotherapy ($p<0.001$), and time to radiotherapy ($p=0.026$), however all differed by whether the patient had no, minor, or major complications, with an increasing trend seen across the three groups (no complications 50 days [IQR 39-63]; minor complications 56 days [IQR 42.5-69]; major complications 57 days [IQR 46-73], supplementary table 4). Furthermore, patients experiencing complications were significantly more likely to experience significant treatment delays, defined as delays of >90 days for chemotherapy ($n=14$, 3.6% of patients with no complications vs $n=7$, 13.0% of patients with major complications; $p=0.011$) and >8 weeks for radiotherapy ($n=222$, 58.7% of patients with no complications vs. $n=29$, 70.7% of patients with major complications; $p=0.016$, supplementary table 4) than those whose procedures were uncomplicated.

DISCUSSION

Although free-flap reconstruction was associated with a longer time to adjuvant therapy than other procedure types, the absolute differences in time to treatment between the surgical groups is small. This study therefore suggests that IBR does not result in clinically-significant delays in the delivery of adjuvant therapy compared to mastectomy alone. Complications, especially those requiring readmission or further surgery however, are important and patients developing problems, irrespective of the procedure performed, were more likely to experience significant delays to both chemotherapy and radiotherapy in this analysis. The apparent paradox of no treatment delay despite the higher rate of major post-operative complications in the IBR group can be explained by careful patient selection for reconstructive surgery. Patients undergoing IBR were significantly younger and fitter, with fewer 'risk-factors' for complications than patients undergoing mastectomy only and were less likely to require adjuvant treatment than the mastectomy only group. This is because IBR was more likely to be performed following mastectomy for extensive DCIS than for high-risk invasive disease with upfront axillary staging used to determine the likelihood that patients would require adjuvant treatment prior to their reconstructive procedure. This suggests that surgeons are cautious in offering IBR to patients likely to require adjuvant treatment¹⁵. These concerns may reflect the impact of radiotherapy on the cosmetic outcome of reconstruction¹⁶, but may also highlight anxiety about potential delays to adjuvant treatment with surgeons only opting to perform IBR in patients considered low risk. This study provides much-needed evidence to suggest that IBR does not lead to clinically-significant delays in carefully selected low risk patient groups but does highlight that major complications can result in significant treatment delays. This study therefore strongly supports the need for careful patient selection to minimize complications and careful communication of the risks of post-operative problems and the potential oncological implication of complications on treatment delays with patients considering surgery. The higher risk of complications in patients undergoing bilateral surgery will particularly inform discussions with patients wishing to undergo simultaneous contralateral risk-reducing mastectomy and gives a sound rationale for delaying such surgery if adjuvant therapy is anticipated, particularly in implant-based reconstruction.

The findings of this study are consistent with other work suggesting that post-operative complications, rather than procedure type, are the main predictor of adjuvant treatment delays⁸. This focuses attention on the need to reduce complications to improve outcomes for patients and is particularly relevant as reconstruction rates are increasing¹⁷. Despite more procedures being performed, however,

1 complications rates appear to be rising with re-operation for complications more than double that seen
2 in the UK National Mastectomy and Breast Reconstruction Audit (NMBRA)⁵. This is a cause for concern
3 as complications not only delay delivery of adjuvant treatments and but may also adversely impact long-
4 term oncological outcomes by promoting a systemic inflammatory response¹⁸. Implant-based
5 procedures are now the most commonly-performed technique^{19,20} and although data from the NMBRA
6⁵ and the National Surgical Quality Improvement Program²¹ suggest implant reconstruction may be
7 associated with fewer complications than other techniques, this study suggests that complications
8 following implant-based and autologous reconstruction are broadly comparable. Reasons for this
9 require further evaluation but may reflect the recent adoption of single-stage direct-to-implant mesh-
10 assisted reconstruction in the UK²² which may be associated with higher complication rates than the
11 traditional 2-stage procedures²³ favoured in the US²⁰. Risk factors for complications, including smoking
12 and high BMI are consistent with those previously reported^{24,25} and highlight the importance of careful
13 patient selection if post-operative problems are to be avoided.

14 This is the first large prospective multicentre study to explore the impact of IBR on time to adjuvant
15 therapy, but it has limitations. Firstly, this is an observational study and risk of bias must be considered.
16 Consecutive patients undergoing mastectomy were recruited from participating centres but there were
17 baseline differences in the treatment groups. Whilst it was possible to adjust for confounding factors
18 such as age, BMI, smoking and ASA grade in the regression analyses, it is acknowledged that it is not
19 possible to identify and control for all potential confounders which may have impacted the results. The
20 study included patients from 76 centres across the UK and Europe and it is the largest study of its kind,
21 but it is possible that participating units differed from those not taking part. However, this is unlikely, as
22 almost half of all the breast and plastic surgical units in the UK elected to participate. A further
23 consideration is that by only reporting delay to initiation of treatment, this study may underestimate both
24 the overall complication rate of IBR and the true impact of reconstruction on the delivery of adjuvant
25 therapy. This is particularly relevant for patients having implant reconstruction who may develop
26 infection whilst receiving chemotherapy requiring treatment to be modified or stopped completely and
27 the implant removed. Following patients during adjuvant treatment was not feasible with the trainee
28 collaborative study design, but new collaborations with oncology trainees will allow these issues to be
29 addressed in the future. Finally, this short-term study does not allow the long-term oncological impact
30 of post-operative complications or any delays in the delivery of adjuvant therapy to be assessed. A
31 data-linkage study to explore long-term oncological outcomes at five and ten years is planned, allowing

1 these important questions to be addressed. Therefore, while it is not possible to establish causality with
2 an observational study design, RCTs in this setting are not possible and the iBRA-2 study provides
3 much-needed evidence to support decision-making for IBR when adjuvant treatments may be needed.

4 The development of post-operative complications rather than the type of procedure performed have
5 emerged as the key determinant of delays to the delivery adjuvant therapy in this study. Immediate
6 implant-based and free-flap reconstructions, however, are associated with significantly higher rates of
7 major complications than mastectomy alone and this is an important finding that should be fully
8 discussed with patients considering reconstructive surgery. Avoiding IBR in high-risk patients including
9 smokers and those with a high BMI and not performing unnecessary bilateral surgery may represent a
10 simple strategy for reducing post-operative problems but this approach needs balanced against patients'
11 desire for IBR. Accurate and balanced communication of risks and benefits is a vital part of shared
12 decision-making ²⁶ and this study provides further evidence to inform this discussion. Major
13 complications, irrespective of the procedure performed, result in delays to adjuvant treatment so
14 strategies to minimise complications are needed for all patients undergoing breast cancer surgery to
15 improve oncological outcomes¹⁸, quality of life²⁷ and minimize the overall cost of care ²⁸. Standardising
16 care may be one strategy by which outcomes may be improved and standardisation is the focus of the
17 UK 'Getting it Right First Time' initiative. [http://gettingitrightfirsttime.co.uk/surgical-specialty/breast-](http://gettingitrightfirsttime.co.uk/surgical-specialty/breast-surgery/)
18 [surgery/](http://gettingitrightfirsttime.co.uk/surgical-specialty/breast-surgery/). Other strategies include altering treatment sequencing and routinely using neoadjuvant rather
19 than adjuvant chemotherapy in patients electing to undergo IBR. This approach is safe, and these data
20 show that those having neoadjuvant therapy start their adjuvant therapy sooner. It may also allow
21 patients to address modifiable risk-factors such as obesity or smoking prior to surgery although it is
22 appreciated that these changes may be challenging. Increased use of neoadjuvant endocrine therapy
23 may also have utility in high-risk groups. Neoadjuvant radiotherapy is a novel approach which may
24 provide an alternative treatment pathway in patients in whom radiotherapy is likely to be required ²⁹.
25 More accurately determining which patients may benefit from adjuvant therapy before the start of their
26 breast cancer treatment, however may be the optimal solution and work to develop a more personalized
27 approach using molecular markers and gene signatures is likely to reduce the number of future patients
28 in whom adjuvant treatment may be indicated^{30,31}.

29 Immediate breast reconstruction does not delay the delivery of adjuvant therapy but implant-based and
30 free-flap reconstruction are associated with higher rates of post-operative complications which are
31 associated with treatment delays. Careful patient selection combined with accurate communication of

1 risk are therefore vital if patients are to make fully informed decision about IBR when adjuvant therapy
 2 is likely to be needed. Further strategies to minimise the risk of complications such as increased use of
 3 neoadjuvant treatment may also be beneficial in this group. This study provides important information
 4 about the risk and impact of complications in IBR to help patients and surgeons make more informed
 5 decisions about their treatment options.

6 **ADDITIONAL INFORMATION**

7 **Ethical approval and consent to participate**

8 This study was classified as service evaluation by the UK National Health Service Research Authority
 9 Decision Tool (<http://www.hra-decisiontools.org.uk/research/index.html>) so individual patient consent
 10 was not required. Local audit department approvals were obtained at each participating centre prior to
 11 commencing patient recruitment.

12 **Data availability**

13 The datasets generated during and/or analysed during the current study are not publicly available due
 14 to ongoing analyses but are available from the corresponding author on reasonable request.

15 **Conflict of interest**

16 The authors have no conflicts of interest to declare.

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25 **Authors' contributions**

26 RLOC, TR and RVD contributed to the study design, data collection and interpretation of results; MG
 27 contributed to study design and coordinated data collection; AT performed the analysis, contributed to

data interpretation and drafted the manuscript; JS and NLPB contributed to study design, data collection and interpretation, AH contributed to study design and interpretation; CH and SP conceived the study and led on the study design and conduct and the interpretation of the results. SP led on the analysis and wrote the first draft of the paper. All authors read and approved the final manuscript.

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Figure legends

Figure 1: Kaplan-Meier analyses for time from last oncological surgery to first adjuvant treatment by 1a) procedure type (left), 1b) whether or not the patient developed post-operative complications (right)