Journal of Radiotherapy in Practice

Journal of Radiotherapy in Practice 2006
5, 203–210

doi: 10.1017/S146039690600029X

Original Article

Implementation and experiences of an intraoperative radiotherapy service

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Abstract

Intraoperative radiotherapy (IORT) using a miniature X-ray source has the potential to impart the same clinical benefit as external beam radiotherapy (EBRT), in a single fraction. The patient benefits are significant, since IORT could replace several weeks of fractionated EBRT. We present our initial experiences of IORT using the Zeiss Intrabeam™ system for treating early stage breast cancer and intracranial malignancies. Implementing this treatment modality requires a multidisciplinary approach drawing on the expertise of surgeons, oncologists, medical physicists, anaesthesiologists, nursing staff and pathologists. Team coherence is facilitated by a nurse co-ordinator. We have treated 66 patients in 24 months. For breast tumours, the mean treatment time was 28.54 min and the applicator sizes ranged from 3.0 to 5.0 cm (mode = 4.5 cm). A dose of 5 Gy is prescribed to spherical volume of 1 cm from the applicator surface. For brain tumours, the mean treatment time was 19.70 min and the applicator sizes ranged from 1.5 to 3.5 cm (mode = 2.5 cm). Mean dose was 11.1 Gy prescribed to a spherical volume of 0.5 cm from the applicator surface.

A multidisciplinary team is essential for the successful implementation of IORT. This paper describes how, through reliance on an oncology nurse specialist to co-ordinate the programme, we have successfully set-up an IORT service.

Keywords

Intraoperative radiotherapy service; breast cancer; photon radiosurgery system; Intrabeam™

INTRODUCTION

Intraoperative radiotherapy (IORT) is a method by which radiotherapy is delivered as a single, high dose in the operating theatre immediately after surgical resection of a tumour.[1] It is scientifically established that the relative biological effectiveness (RBE) of photons increases with decreasing photon energy. As the energy of the photons decreases, the energy of the secondary electrons emitted in the photon interactions decreases, with a corresponding increase in stopping power or linear energy transfer. Other researchers have shown that RBEs at clinically relevant doses for low-energy X-ray sources (XRSs) are considerably greater than unity, both relative to ^{60}Co and to ^{192}Ir photons.[2,3] That is, the approximate physical IORT dose can be multiplied by a factor greater than 1 to determine the biologic effects.[4] This increased RBE results in decreased dose and exposure time necessary to yield the same biological effect.

The past 20 years have seen a distinct shift in the paradigm used in the treatment of breast cancer,

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away from radical interventions toward more conservative techniques such as IORT. Randomised clinical trials have shown that breast conserving surgery allied to external beam radiotherapy (EBRT) compares favourably with more radical procedures such as mastectomy. Intracerebral metastases are common and occur in up to 15% of cancer patients.[5] The survival rates for malignant gliomas are only about 7.5% at 2 years.[6] The majority of relapses occur locally indicating that a more radical local treatment may offer a higher probability of success.[7]

Ninewells Hospital has acquired four Zeiss Intrabeam™ IORT treatment systems (Carl Zeiss AG, Oberkochen, Germany) used to treat breast and brain tumours. Each consists of a microprocessor based control console (PRS400), miniature XRS, mobile gantry and a range of quality control tools. This paper describes our methods of implementation and subsequent experience with this promising new radiotherapy technique.

METHODS

Device description

The key component of the Intrabeam™ System is a portable X-ray generator capable of delivering, during a surgical procedure, the prescribed therapeutic radiation dose directly to the tumour bed. The device itself weighs 1.62 kg, has dimensions 17.5 × 11 × 7 cm with a 3.2 × 100 mm chromium nitride coated probe and is powered by a portable, electronic control console. These XRSs generate very low-energy X-rays, up to 50 kV (0.1 mm Al, half value layer), and the dose fall-off is rapid, ($\sim 1/r^3$). The electron beam is accelerated through a high-voltage field (range 30–50 kV) and then passes through a deflection chamber, which controls beam position and straightness. The beam current, which affects the amount of radiation produced per unit of time, is selectable (5, 10, 20 and 40 μA). After travelling down the evacuated, magnetically shielded probe, the electron beam strikes a thin gold target (1 μm) at the probe tip producing X-ray photons whose mean effective energies are typically in the range of 5–20 keV (at 50 kV, 40 μA). The distal 20 mm of the probe is fabricated from beryllium (0.5 μm), which is transparent to very low-energy X-ray photons. The X-rays are emitted from the probe tip in a spherical, symmetrical pattern resulting in a dose rate in tissue of approximately 2 Gy/min at 10 mm from the probe tip.[8] Figure 1 shows the miniature XRS mounted on the arm of the mobile gantry.

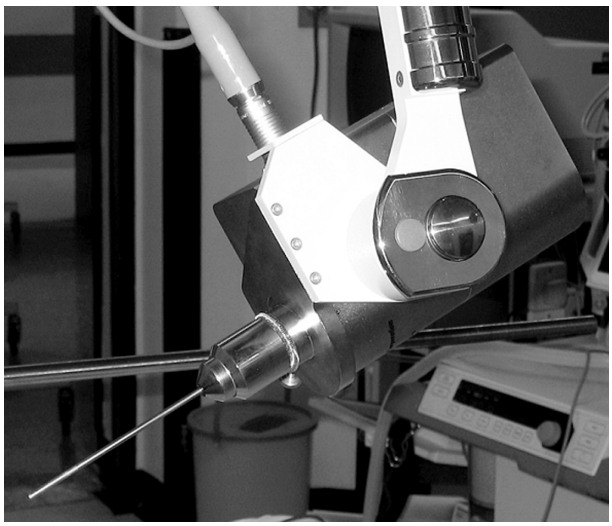

Figure 1 XRS mounted on mobile gantry.

During treatment delivery, the entire probe is enclosed by a conical sheath at the end of which is a spherical applicator made of polyetherimide ($C_{37}H_{24}O_6N_2$). This has a glass transition temperature of 216°C, a density of 1.27 g · cm^{-3}, is biocompatible and radiation resistant. A range of applicator sizes, from 1.5 to 5.0 cm in diameter, is available for various sizes of tumour bed.

Patient selection – breast

Patients aged 40 or older with operable, invasive breast cancer (T1–3, N0–1, M0) confirmed by cytological or histological examination and who are suitable for breast conserving surgery are considered for the clinical trial. Patients are randomised prior to surgery after being fully informed about the trial and have given written consent. Exclusion criteria include cases where there is evidence of bilateral breast cancer at the time of diagnosis, more than one obvious cancer in the same breast, patients presenting with gross nodal disease and those with extensive lobular cancer. Patients undergoing primary medical treatment such as hormonal or chemotherapy and those with any severe concomitant disease that may in any case, limit their life expectancy are also excluded.

https://doi.org/10.1017/S146039690600029X Published online by Cambridge University Press

All patients have a wide local excision (WLE) of the primary tumour following the appropriate clinical workup. The depth of the excision always includes the pectoralis fascia so that there is no breast tissue beyond the deep margin.[9] Haemostasis must be ensured since even a small haemorrhage can accumulate a significant amount of fluid at the treatment site and distort the tumour cavity. The applicator is inserted into the cavity and the wound is closed around the shaft of the applicator using a purse-string stitch. The surgeons must ensure that no part of the skin is within 1 cm of the surface of the applicator to ensure skin sparing. The applicator is then coupled with the XRS, which itself is attached to the balanced gantry and controller.

Patient selection – brain

Patients diagnosed with intracranial primary or single secondary malignant tumours are considered for IORT. Diagnosis is made on the basis of contrast enhanced CT or MRI scans.[10] The local inclusion criteria are that the patient must be 17 or older, have a particular type of malignancy (glioblastoma multiforme, anaplastic gliomas, anaplastic oligodendroglioma, or single brain metastasis) and a Karnofsky Performance Scale >60. Eligible patients have the procedure explained to them and must give written consent before being randomised for the high- or low-dose group. As the survival rate of patients with malignant intracranial tumours is very short (6–12 months), they are followed up clinically and radiologically according to current local practice.[11] Outcome is determined 2 weeks after discharge, followed by 3-monthly checks for the first year, reducing to 6-monthly later. A booster dose may be considered for cases where there is tumour progression or recurrence.

Skill requirements for IORT delivery – the multidisciplinary team

The key members of an effective IORT team include the surgeon, radiation oncologist, medical physicist, pathologist, anaesthetist and nursing staff.[12] Although the basic concept of IORT is simple, the complexity arises where professionals from different disciplines are involved in this highly collaborative framework. In addition to medical staff, two essential roles involve medical physicists and an IORT oncology nurse specialist. Liaison amongst the interdisciplinary team is facilitated by the IORT Nurse co-ordinator to ensure effective dialogue, which is essential for the team to provide a patient-centred service. However most importantly, the role of the IORT Nurse Co-ordinator is to support the patient and colleagues through the whole process by trouble shooting and addressing any issues that may arise.

Patient positioning and immobilisation

Patients normally undergo treatment under general anaesthetic. For breast cancer patients, no special immobilisation techniques are usually required. However, for patients with heavy breasts where there is a tendency for lateral displacement with the patient supine, we have used a custom built support to minimise such movement. For brain treatments, the patients' head is fixed in a Mayfield head clamp and the applicator is positioned in the tumour bed with the aid of image guidance.

Treatment delivery

The physicists first perform an output verification of the XRS in the operating theatre. The surgeon then ascertains the most suitable sized applicator to fit the tumour bed. This is used to perform the treatment time calculation whilst the surgeon inserts the applicator and arranges flexible, sterile lead shielding around the treatment site. The physicists then ensure the operating theatre becomes a controlled area before commencing treatment. The treatment is continuously monitored by the physicists who are also able to pause the treatment should the anaesthetist need to intervene.

Quality assurance

A pre-treatment verification is carried out within 24 h of the IORT equipment being required in the operating theatre. The procedure is based on the manufacturer's recommendations and consists of a probe adjust test, isotropy adjust, a test of the internal and external radiation monitors (IRM, ERM) and a measurement of the X-ray field strength. During the pre-treatment checks,

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machine interlocks, emergency stop, treatment pause, audible X-rays on warning and the mechanical integrity of the XRS are all verified.

As part of a service agreement with the manufacturer, each XRS is returned for a full recalibration every year and a calibration certificate is issued by the Physikalisch Technische Werkstatt (Freiburg, Germany). The certificate contains a new ion chamber calibration factor (N_x) along with a depth–dose curve showing the variation in dose rate at distances from 3 to 45 mm away from the probe tip. Good practice requires that an independent measurement is made of the depth–dose curve and compared to the manufacturer's data.[13]

Radiation protection measures

It has been suggested that due to the rapid attenuation in air, IORT can be performed without additional shielding for theatre staff.[14,15] However, to comply with Ionising Radiation Regulations 1999[16] and UK Health and Safety Regulations,[17] an independent, in-house risk assessment was performed prior to the Intrabeam™ system being used clinically. Radiation surveys were performed on four operating theatres during simulated IORT treatments with no patient present but using a suitable phantom.

To protect staff we use mobile lead-glass screens, (Wardray Premise, Surrey, UK – 2 mm Pb equivalent). We also investigated the attenuation properties of a flexible lead (0.5 mm Pb equivalent) shielding for use at the treatment site.[18] Measurements were made to determine the gross percentage attenuation of 50 kV peak radiation through various parts of the same shield. In addition to these protection measures, we regularly perform environmental surveys during treatment to monitor radiation levels.

In terms of personal protection, physicists supervising the treatment delivery wear optically stimulated luminescence film badges able to detect photon energies above 5 keV. Electronic personal dosemeters are also utilised as these provide an immediate indication of the levels of radiation in the vicinity. During radiation surveys of the theatre during treatment, a full lead apron was also worn. The time spent performing the surveys is minimised and care is taken to remain as far away from the XRS as possible.

RESULTS

Early stage breast cancer

We have treated 46 patients with early stage breast cancer who were suitable for breast conserving surgery. Table 1 shows the IORT treatment details for these patients. Their ages ranged from 42 to 81 years (mean = 62.3). The intent was adjuvant in 18 cases and radical in 28 cases. The operating parameters for the XRS were 50 kV and 40 μA in all cases, and the mean treatment time required to deliver the prescribed dose of 5 Gy to 1 cm from the surface of the applicator was 28.54 min. The most frequently used applicator sizes were 4.5 and 5.0 cm (16 cases each). These patients are part of the multi-centre Targit clinical trial, which is ongoing.

Invasive intracranial malignancies

We have also treated 20 patients with invasive intracranial malignancies. So far, 6 patients have been randomised to the high-dose group and 14 to the low-dose group. Table 2 shows the IORT treatment details for these patients. Their ages ranged from 32 to 82 years (mean = 60.1). The intent was palliative in 9 cases and radical in 11 cases. The operating parameters for the XRS were 50 kV and 40 μA in all cases, and the overall mean treatment time was 19.70 min. The smallest applicator used had a diameter of 1.5 cm and the largest was 3.5 cm. The most frequently used applicator size was 2.5 cm (6 out of 20 cases).

Equipment performance

We have conducted an extended investigation of the output of each XRS to determine the performance reproducibility of the sources. They have proven to be stable over time and most measurements were found to lie within the manufacturer's tolerances. An intercomparison of the four sources showed that they have similar performance characteristics.[19]

Radiation protection

Measurements of the ambient dose equivalent rate showed that at 1 m away from the treatment site

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Table 1. IORT treatment details for patients with early stage breast cancer

No.	Applicator (cm)	Breast site	Intent	Age	Dose @ 1 cm in (Gy)	IORT time (min)	Cumm photon count	Average photon count
1	3.0	R	Adjuvant	47	5.0	21.89	94,800,000	4,331,734
2	5.0	R	Adjuvant	64	5.0	35.86	154,800,000	4,316,426
3	5.0	L	Adjuvant	43	5.0	35.32	154,000,000	4,360,753
4	5.0	L	Adjuvant	63	5.0	34.06	148,100,000	4,347,698
5	4.5	L	Adjuvant	55	5.0	29.22	126,400,000	4,325,360
6	4.5	R	Adjuvant	63	5.0	29.01	126,400,000	4,356,818
7	5.0	R	Adjuvant	63	5.0	36.46	158,600,000	4,350,569
8	4.5	R	Adjuvant	49	5.0	28.89	126,200,000	4,368,445
9	5.0	L	Adjuvant	58	5.0	35.70	155,700,000	4,361,345
10	5.0	R	Adjuvant	70	5.0	35.88	155,600,000	4,337,040
11	4.5	R	Adjuvant	75	5.0	29.07	126,200,000	4,341,245
12	5.0	L	Adjuvant	76	5.0	35.31	153,600,000	4,350,042
13	5.0	R	Adjuvant	64	5.0	35.57	154,100,000	4,332,303
14	4.5	R	Adjuvant	63	5.0	26.60	150,500,000	5,657,895
15	3.5	R	Adjuvant	49	5.0	16.79	94,780,000	5,645,027
16	5.0	L	Adjuvant	54	5.0	32.33	182,000,000	5,629,446
17	5.0	L	Radical	54	5.0	32.87	183,700,000	5,588,683
18	4.0	L	Radical	74	5.0	21.12	119,000,000	5,634,470
19	5.0	L	Radical	67	5.0	32.41	181,000,000	5,584,696
20	4.5	R	Radical	63	5.0	26.67	149,700,000	5,613,048
21	4.0	R	Radical	45	5.0	21.51	120,900,000	5,620,642
22	4.0	L	Adjuvant	79	5.0	21.60	120,500,000	5,578,704
23	4.5	L	Radical	81	5.0	26.69	150,400,000	5,635,069
24	4.0	L	Adjuvant	70	5.0	21.65	121,200,000	5,598,152
25	4.0	L	Radical	71	5.0	21.73	121,200,000	5,577,543
26	4.5	L	Radical	53	5.0	26.91	150,700,000	5,600,149
27	4.5	L	Radical	73	5.0	28.77	139,100,000	4,834,897
28	3.5	L	Radical	70	5.0	18.46	89,400,000	4,842,904
29	4.5	R	Radical	47	5.0	29.28	139,600,000	4,767,760
30	4.5	R	Radical	51	5.0	29.79	139,800,000	4,692,850
31	3.5	R	Radical	64	5.0	16.81	94,700,000	5,633,551
32	5.0	R	Radical	67	5.0	32.53	184,200,000	5,662,465
33	4.5	L	Radical	63	5.0	26.74	150,300,000	5,620,793
34	3.5	L	Radical	69	5.0	16.98	73,600,000	4,334,511
35	4.5	R	Radical	65	5.0	26.49	115,200,000	4,348,811
36	4.0	L	Radical	69	5.0	21.73	94,300,000	4,339,623
37	5.0	L	Radical	70	5.0	33.11	182,500,000	5,511,930
38	4.5	L	Radical	63	5.0	26.65	151,000,000	5,666,041
39	4.5	R	Radical	55	5.0	26.58	149,700,000	5,632,054
40	4.0	L	Radical	48	5.0	21.13	91,700,000	4,339,801
41	4.5	L	Radical	50	5.0	26.53	114,700,000	4,323,407
42	3.5	L	Radical	53	5.0	18.56	82,000,000	4,418,103
43	5.0	R	Radical	68	5.0	34.81	153,100,000	4,398,161
44	4.0	R	Radical	72	5.0	22.38	99,200,000	4,432,529
45	5.0	R	Radical	62	5.0	33.17	184,400,000	5,559,240
46	5.0	R	Radical	75	5.0	33.25	184,500,000	5,548,872

Applicator size (cm)	Times used		IORT time (min)	Cumm photon count	Average photon count
3.0	1	Mean	28.54	136,806,087	4,964,165
3.5	5	SD	5.96	30,432,493	610,634
4.0	8	95% CI	1.72	8,794,397	176,461
4.5	16	LCL	26.82	128,011,690	4,787,704
5.0	16	UCL	30.26	145,600,484	5,140,627
Total	46	Median	29.07	143,950,000	4,801,329
		Min	16.79	73,600,000	4,316,426
		Max	36.46	184,500,000	5,666, 041

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Table 2. IORT treatment details for patients with invasive intracranial malignancies

No.	Applicator (cm)	Brain site	Intent	Age	IORT dose @ 0.5 cm in (Gy)	IORT time (min)	Cumm. photon count	Average photon count
1	1.5	R	Palliative	48	15.0	15.60	75,600,000	4,845,843
2	2.5	L	Radical	71	12.0	23.98	116,300,000	4,849,673
3	3.0	L	Radical	68	8.0	20.62	100,600,000	4,879,705
4	2.0	L	Radical	69	12.0	17.39	83,800,000	4,818,584
5	2.0	L	Palliative	55	12.0	17.28	84,190,000	4,871,543
6	3.0	R	Palliative	82	8.0	20.92	101,400,000	4,846,110
7	2.5	R	Palliative	53	12.0	24.45	117,000,000	4,784,885
8	1.5	R	Radical	64	15.0	15.07	73,370,000	4,868,290
9	2.5	L	Palliative	56	8.0	16.10	77,560,000	4,817,691
10	3.5	R	Palliative	61	10.0	21.39	104,100,000	4,866,760
11	2.5	R	Palliative	64	15.0	29.04	141,100,000	4,858,648
12	3.5	R	Radical	57	8.0	17.86	84,890,000	4,752,281
13	2.0	R	Radical	73	15.0	22.02	106,500,000	4,836,512
14	3.0	L	Radical	37	8.0	19.83	85,800,000	4,326,778
15	3.0	L	Palliative	74	8.0	19.70	85,300,000	4,329,949
16	2.0	R	Radical	44	12.0	16.33	71,050,000	4,350,888
17	3.0	L	Radical	64	8.0	19.68	84,800,000	4,308,943
18	3.5	R	Radical	32	10.0	22.11	98,100,000	4,436,906
19	1.5	R	Palliative	60	12.0	12.47	60,000,000	4,811,548
20	2.5	L	Radical	68	12.0	22.05	124,100,000	5,628,118

Applicator size(cm)	Times used		IORT time (min)	Cumm. photon count	Average photon count
1.5	2	Mean	19.70	93,778,000	4,754,483
2.0	4	SD	3.84	20,197,818	299,057
2.5	6	95% CI	1.68	8,851,908	131,065
3.0	5	LCL	18.01	84,926,092	4,623,418
3.5	3	UCL	21.38	102,629,908	4,885,547
Total	20	Median	19.77	85,550,000	4,827,548
		Min	12.47	60,000,000	4,308,943
		Max	29.04	141,100,000	5,628,118

and without shielding, the dose rate was of the order of 10 $mSv \cdot h^{-1}$, (treatments may last up to 40 min). The measured dose rate was found to be less than 2 $\mu Sv \cdot h^{-1}$ behind lead screens placed 1.5 m away from the treatment site. It was found that a single thickness of flexible lead shielding provided greater than 99% effective attenuation at this clinical energy. The lead shielding can also be cut into specific shapes to adequately cover the treatment site and is now used during all IORT procedures.

We have found that despite the precautionary measures taken, there are still radiation 'hot spots' present in the operating room during treatment delivery. These dose rates can be up to 2.0 $mSv \cdot h^{-1}$ and their exact locations vary in the operating theatre. We have surmised that these 'hot spots' are the result of non-uniform shielding at the treatment site due to the topography of the local skin surface. To reduce the occurrence of these 'hot spots' we have iteratively modified the basic shape of the shielding to provide optimal coverage of the treatment site.

DISCUSSION

Staff acceptance and additional resources

As with all new technology, there was some initial scepticism as to the effectiveness of IORT. It is accepted that IORT significantly increases the time the patient spends in theatre under full anaesthetic and therefore increases the overall clinical risk. To match an ever-increasing surgical load, the efficiency of use of operating theatres must improve. It is within the remit of the medical physicist to explain to theatre staff, the physics

https://doi.org/10.1017/S146039690600029X Published online by Cambridge University Press

behind the procedure and impart reassurance on radiation protection concerns. Staff acceptance has increased with the number of patients treated.

Physicist resources

In terms of additional physics staffing resources, we estimate that it may not be feasible for existing physics staff to fully support a comprehensive IORT program. Before each treatment, the performance of the XRS must be verified. Two medical physicists typically spend 2 h in theatre and the pre-treatment verification requires 1 h, this amounts to 5 physics-hours per procedure. A full service performing six procedures per week would require 30 physics-hours (0.80 whole time equivalent). This places an additional, quantifiable burden on existing staff.

Potential benefits of IORT

While the benefits to patients undergoing IORT are clear – accurate dose delivery, much shorter treatment and superior cosmesis – the inherent benefits for the National Health Service (NHS) should not be understated. Breast cancer accounts for 30% of all cancers in women. The latest survival figures for England show that an average of 76% of women diagnosed with breast cancer in 1993–1995 were alive 5 years later.[20] This increase in survival rate is probably due to a combination of improved screening and new treatment techniques. IORT has the potential to be one such technique by reducing waiting times for breast cancer treatment and facilitating more efficient use of radiotherapy resources. These in turn could translate to significant cost savings for the NHS.

The Scottish Executive Health Department further states that 'if IORT replaces EBRT for early breast cancer this would have a profound affect on the requirement for machine capacity'.[21] The Scottish Executive has recognised that 'modern management of cancer requires the collaboration of professionals from many different disciplines'.[22] With the development of a new IORT service there is a considerable amount of co-ordinated work involving surgery, physics, radiation oncology, pathology and nursing. Co-ordination of such a project is not inconsiderable and includes utilising existing resources and a blurring of interdisciplinary boundaries.

CONCLUSION

A multidisciplinary team working with a team co-ordinator is essential for the successful implementation of any new treatment such as IORT. IORT has proven to be feasible and safe in the two clinical areas we have used it in, breast and brain. We have described how, through reliance on an oncology nurse specialist to co-ordinate the programme, we have successfully setup an IORT service. Our experience could serve as a model for introducing this new radiotherapy technique into the management of patients with cancer at other centres.

ACKNOWLEDGEMENTS

The authors wish to acknowledge the continuing support of the Ninewells Cancer Campaign. We would also like to acknowledge our colleagues also involved in the clinical trial: John Parry, Colin Mackay, Salam Souliman, Dougal Adamson, Douglas Brown, John Dewar, Jayant Vaidya, Alastair Thompson, Robert Wood and Alastair Munro.

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https://doi.org/10.1017/S146039690600029X Published online by Cambridge University Press