

Advances in Testicular Cancer

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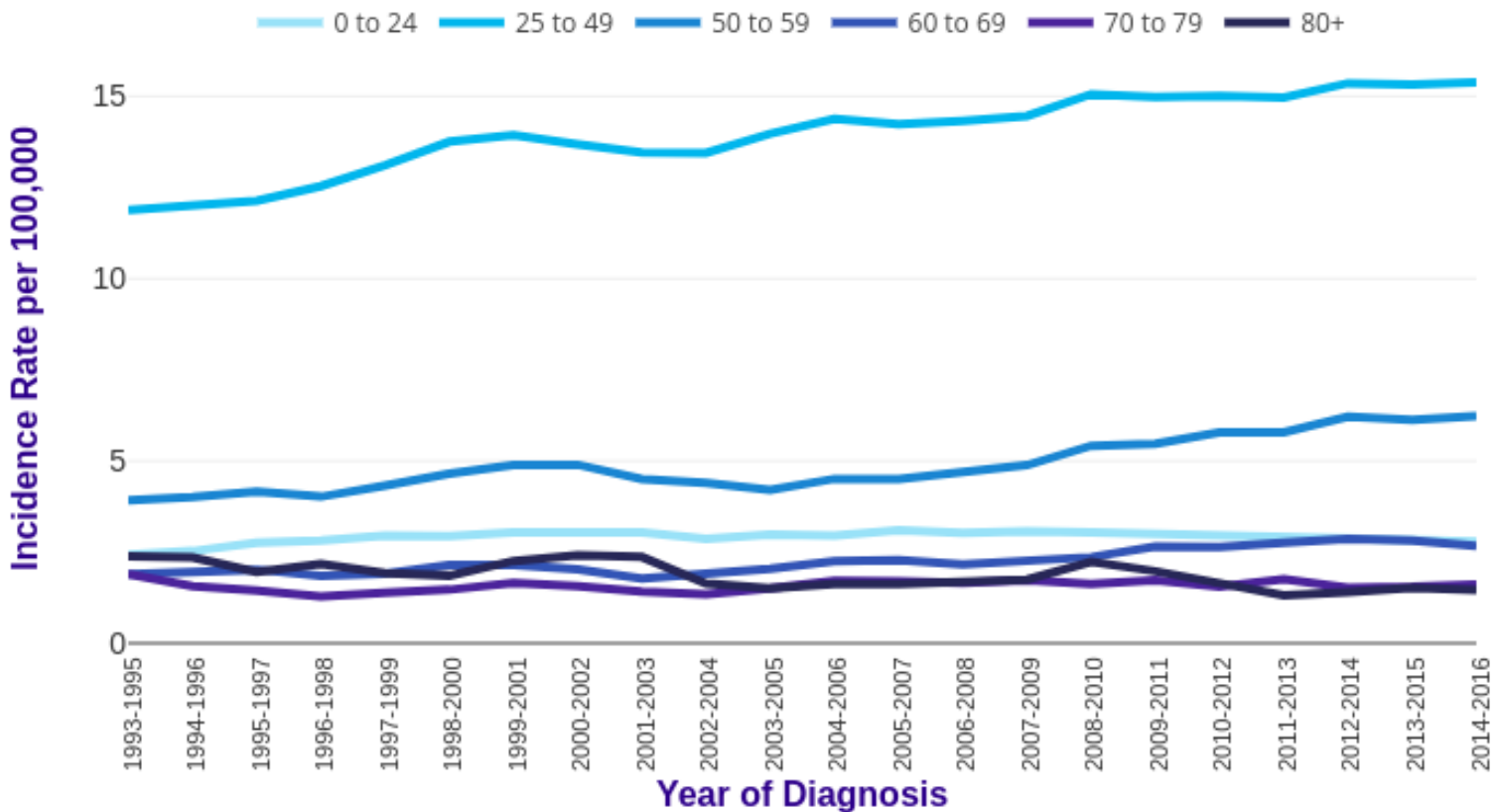
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Testicular Cancer

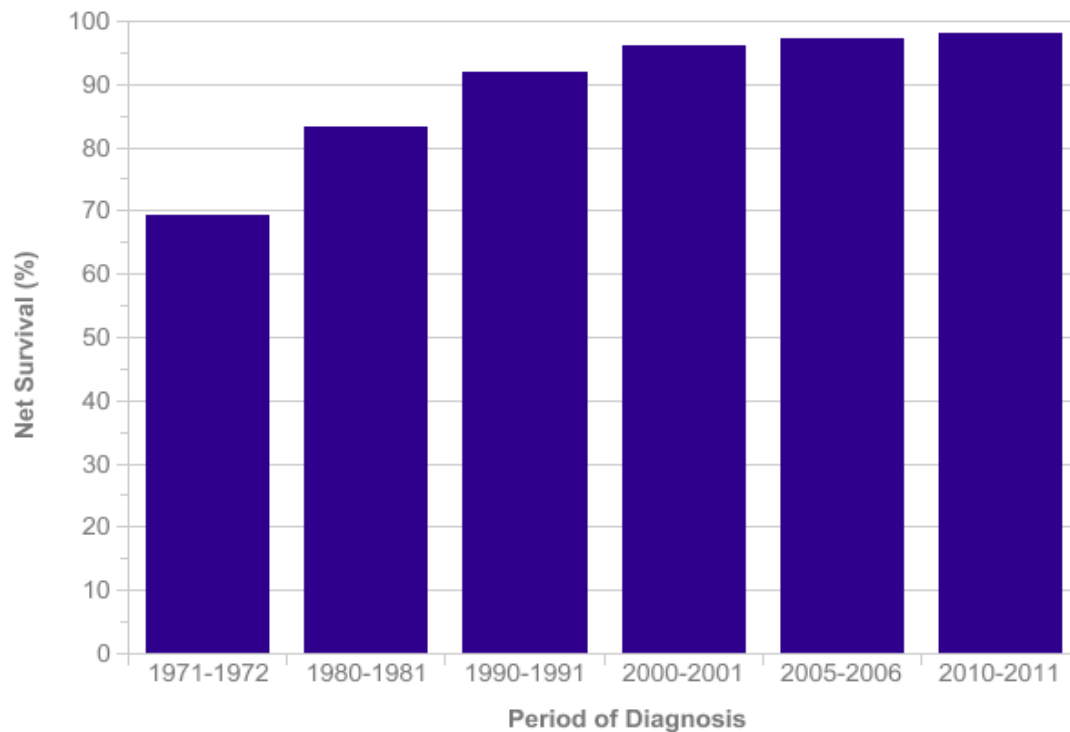


- Approx. 2,400 new cases of testicular cancer in the UK in 2016 (7 cases diagnosed every day).
- Testicular cancer accounts for less than 1% of all new cancer diagnoses in the UK (2016).
- In males in the UK, testicular cancer is the 16th most common cancer.
- Incidence rates for testicular cancer in the UK are highest in males aged 30-34 (2014-2016).
- 1 in 215 males born in the UK after 1960 will be diagnosed with testicular cancer during their lifetime.
- 57 deaths from testicular cancer in the UK in 2016.

Testicular cancer age-standardised incidence rates, males, UK, 1993 to 2106



Testicular Cancer (C62): 1971-2011
Age-Standardised Ten-Year Net Survival, England and Wales



Poor prognostic GCT remains accountable for the greatest average number of years of life lost of any adolescent or adult malignancy

Seer database, 2007

Concepts

- Confidence in management
- Reduce burden of treatment in early stage disease
 - TE19/TE24/BEP111
- Better understanding biology (molecular markers) & biological differences (sites/age/gender)
 - Immunohistochemistry of primordial germ cells, potential targets selective inhibition
 - Epigenetics, e.g. decreased methylation
 - Age – GCNIS
 - Female
 - 75-110 cases per year in UK, usually <20yrs old
 - Relapsed disease poorer outcomes than males

Concepts

- Better understanding inheritance & biological effects
 - No germ-line mutation identified
 - familial clustering – weak predispositions, shared in utero and postnatal risk factors, coincidental somatic mutations
 - Testicular dysgenesis
 - Hypospadias, cryptorchidism, poor semen quality, testicular germ cell tumour
- Global co-operation in rarer presentations, poor prognosis, salvage.

Current Management

- ESMO Consensus Conference November 2016, published Annals Oncology 2018.
- Current practice
- Recent studies
- Areas of active interest

Treatment decisions

- Histology
 - Seminoma vs non-seminoma
- Stage
 - RMH staging
- Prognostic group
 - IGCCCG
- First presentation/relapse
 - Platinum sensitivity
- Co-morbidities
 - Upfront vs relapse treatment

Histology – WHO update 2016

British TTP&R

WHO

Germ cell neoplasia in situ

Seminoma

Seminoma

Spermatocytic seminoma

Spermatocytic tumour

Non-seminomatous GCT

Teratoma

Malignant teratoma differentiated

Teratoma

Malignant teratoma intermediate

Malignant teratoma undifferentiated

Yolk sac tumour

Embryonal carcinoma

Yolk sac tumour

Malignant teratoma trophoblastic

Choriocarcinoma

Pathological staging

- American Joint Committee on Cancer (AJCC)
Eighth TNM version
 - e.g. seminoma pT1a <3cm and pT1b for tumours \geq 3 cm
 - Rete testis invasion remains as T1 disease
- Union for International Cancer Control (UICC)
Eighth edition
 - Not adopted same criteria

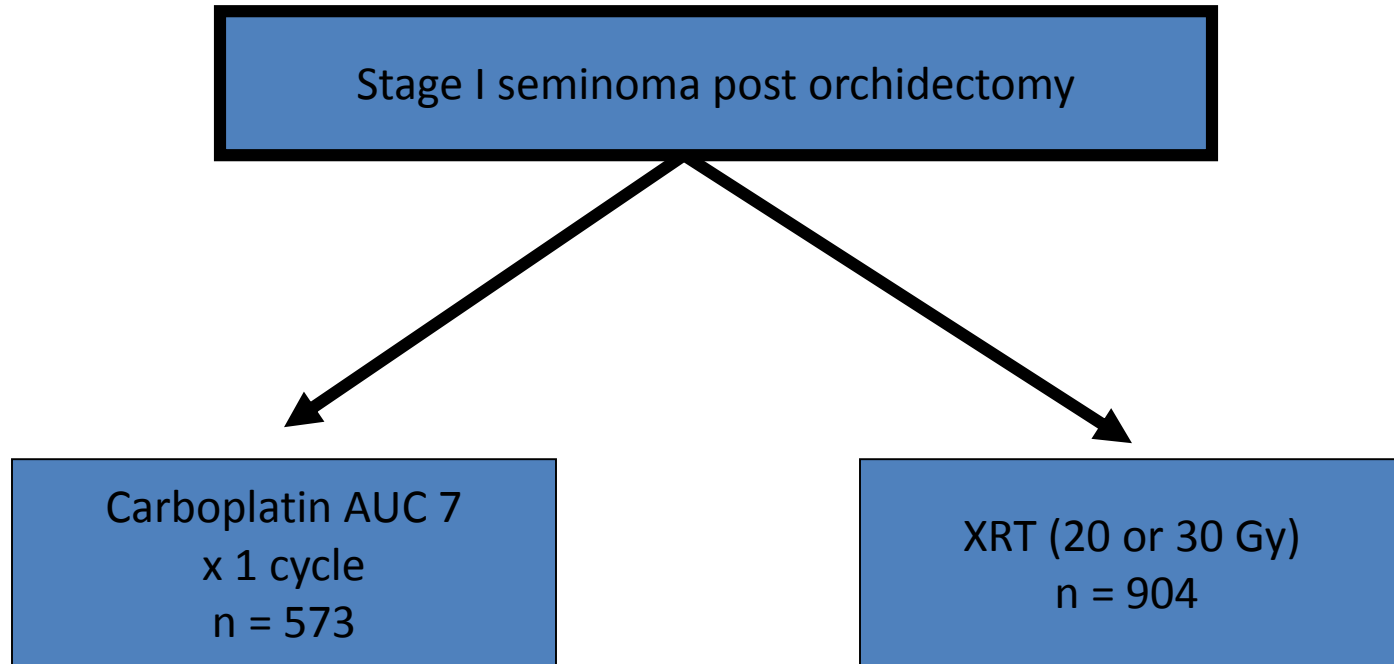
Stage	Definition
I	No evidence of disease outside the testis
IM	As above but with persistently raised post-op tumour markers
II	Infradiaphragmatic nodal involvement
	A Nodes maximum diameter < 2cm
	B Nodes maximum diameter 2-5 cm
	C Nodes maximum diameter 5-10cm
	D Nodes maximum diameter > 10cm
III	Supra and infradiaphragmatic node involvement
	A Abdominal nodes < 2cm
	B Abdominal nodes 2-5cm
	C Abdominal nodes >5cm
	Neck nodes N + Mediastinal nodes M +
IV	Extralymphatic metastases Abdominal nodes A, B, C, as above Mediastinal or neck nodes as for stage 3
	L1 < 3 lung metastases
	L2 Multiple lung metastases < 2 cm maximum diameter
	L3 Multiple lung metastases > 2 cm in diameter
	H+ Liver involvement
	Other sites identified (Br- brain, Bo- bone, Ad- adrenal)

International Germ Cell Consensus
Prognostic Grouping
1997

Update project
EORTC, Silke Gillessen

TERATOMA (NSGCT)	SEMINOMA
GOOD PROGNOSIS with all of:	
Testis/retroperitoneal primary No non-pulmonary visceral metastases AFP < 1000 ng/ml HCG < 5000 iu/l LDH < 1.5 upper limit of normal <ul style="list-style-type: none"> • 56% of teratomas • 5-year survival 92% 	Any primary site No non-pulmonary visceral metastases Normal AFP Any HCG Any LDH <ul style="list-style-type: none"> • 90% of seminomas • 5-year survival 86%
INTERMEDIATE PROGNOSIS with all of	
Testis/retroperitoneal primary No non-pulmonary visceral metastases AFP > 1000 AND < 10000 ng/ml or HCG > 5000 AND < 50000 iu/l or LDH > 1.5 normal < 10 normal <ul style="list-style-type: none"> • 28% of teratomas • 5-year survival 80% 	Any primary site Non-pulmonary visceral metastases Normal AFP Any HCG Any LDH <ul style="list-style-type: none"> • 10% of seminomas • 5-year survival 73%
POOR PROGNOSIS with any of:	
Mediastinal primary or non-pulmonary Visceral metastases AFP > 10,000 ng/ml or HCG > 50,000 iu/l or LDH > 10 normal <ul style="list-style-type: none"> • 16% of teratomas • 5-year survival 48% 	No patients classified as poor prognosis

MRC TE 19 study



1447 patients randomised (3:5 ratio CTx: RTx)
June 1996 – March 2001; median follow up 3
years

Oliver et al Lancet. (2005) 366:293-300.

TE 19

RFS rates	RTx (n=904)	Chemotherapy (n=573)
2 yrs	96.7 %	97.7 %
3 yrs	95.9 %	94.8 %

Relapses	RTx	Chemotherapy
Number	32	27
Pattern	Pelvis, neck, mediastinum	abdominal nodes

TE 19 - Long Term Toxicity

New primary cancers

- Chemotherapy – 2 GCT, 3 other
- RTx – 10 GCT, 4 other

Fertility

- Effect of carboplatin unknown in this setting

TE24

- Stage 1 seminoma, randomised
- Aim
 - Observe potential to reduce radiation exposure during surveillance without adversely affecting outcome
- Rationale
 - Unknown risk of single cycle carboplatin AUC 7
 - Mx stratified (Warde criteria)
 - RMH surveillance 7 CT scans over 5 years (8-20 elsewhere)
 - Risk of secondary malignancy from single chest/abdo/pelvis CT is 1 in 2000, calculated at 1 in 300 if 7 CTs

TE24 continued

- 4 arms
 - CT or MRI, 3 or 7 scans
 - 6 monthly for 2 years, then annually until 5 years
 - or
 - 6/18/36 months
- Closed to recruitment 31.07.2014
- Primary outcome
 - Proportion relapsing \geq IIc disease
- Secondary outcomes
 - Difference in mean size of relapse
 - Time to relapse
 - DFS
 - OS
 - Evaluation of prognostic factors for relapse

BEP111

- Single arm, in stage 1 high-risk NSGCT or mixed histology
 - 1 cycle BE⁵⁰⁰P (standard 2 cycles BE³⁶⁰P)
- Aim – ensure 2-year PFS at least 95%
- Recruited Feb 2010 to July 2014
- N= patients, 33 UK centres
- Median follow-up 39 months
- 2-year recurrence rate 2.6% (4 chemo-sensitive, 3 teratomas)
- Safely deliverable (6.4% FN)

Relapses after adjuvant BEP stage 1 NSGCT

- Retrospective analysis, global cancer group
- N = 51, 18 centres, 11 countries
- 5-year PFS 64%, OS 78%
- Outcomes worse c/f chemo naïve patients with metastatic disease, better than patients relapsed after chemo for metastatic disease.
- Late relapses:
 - 29% relapsed > 3 years after adjuvant treatment
 - Latest relapse >25 years
 - Assoc with statistically significant increased risk death GC cancer
 - Subsequent relapses – 29% after 1st relapse
- Diversity in treatment strategy
 - Consider 3-4# 3 drug regimen, exchange bleomycin for ifosfamide

Accelerated BEP

- Previous strategies to improve 1st line chemo tested in phase II and III trials have included;
 - alternative or additional chemo drugs
 - more complex multi-drug regimens
 - high dose chemo with stem cell support
 - Examples;
 - Induction C-BOP/BEP (2005, 2011), GAMEC (2007), high dose 1st line (2007), BOP/VIP-B (1998), paclitaxel BEP (2012), POM B/ACE (1997), cis/cyclo/dox (2008)
- None improved cure rates, all more toxic than BEP
- 2014 phase II, ANZUP (n=45), UK trial n=16
 - 1st line int/poor prog
- Strategy successful other cancer sites (OS in NHL x2, early breast cancer, SCLC x2)
 - E.g. DLBCL CHOP 3-weekly since 1970s, accelerated to 2-weekly, addition of rituximab

UK P3BEP

- Aligned with ANZUP P3BEP
- 20 UK sites, target recruitment 150
- phase III for pts with intermediate/poor prognosis
GCT of ovary/testis/retroperitoneum/mediastinum
- 1:1 randomisation, standard 3-weekly vs 2-weekly BEP
- Primary aim – PFS
- Secondary aims – OS, delivery dose intensity, treatment preference, QoL, adverse events.

TIGER trial

- Optimising outcome of salvage treatment in relapsed or refractory germ cell tumours.
- Patients with relapsed GCTs
 - 30% relapse, 20% ultimately die of GCT
 - Standard treatment
 - VIP – CR 50%, long-term PFS 25% (unselected patients)*
 - TIP – n=46, phase II, selected patients, CR 70%, PFS 73% at 7 years**
- 1st line salvage high-dose chemo regimens
 - Durable remission in 30-60%
 - Sequential vs single high dose chemo – trial closed due to unacceptable toxicity in single high dose arm***
 - Only 1 RCT c/f conventional chemo (VIP/VeIP) vs high-dose carbo-PEC as 1st salvage tx, but used single rather than sequential high-dose (n=280, no diff OS or PFS)****
 - Matched paired analysis conventional chemo vs high-dose, approx 10% benefit 2-year PFS and OS#
 - Single-centre trials e.g. phase I/II, n=107, TI-CE 3 cycles, selected pts with poor prog features, durable remission approx. 50% at 5-years##
 - Retrospective study, n=1594, 1st line salvage chemo high-dose vs conventional, 2-year PFS 50vs 28%, p<0.001, 5-year OS 53% vs 41%, p<0.001.###

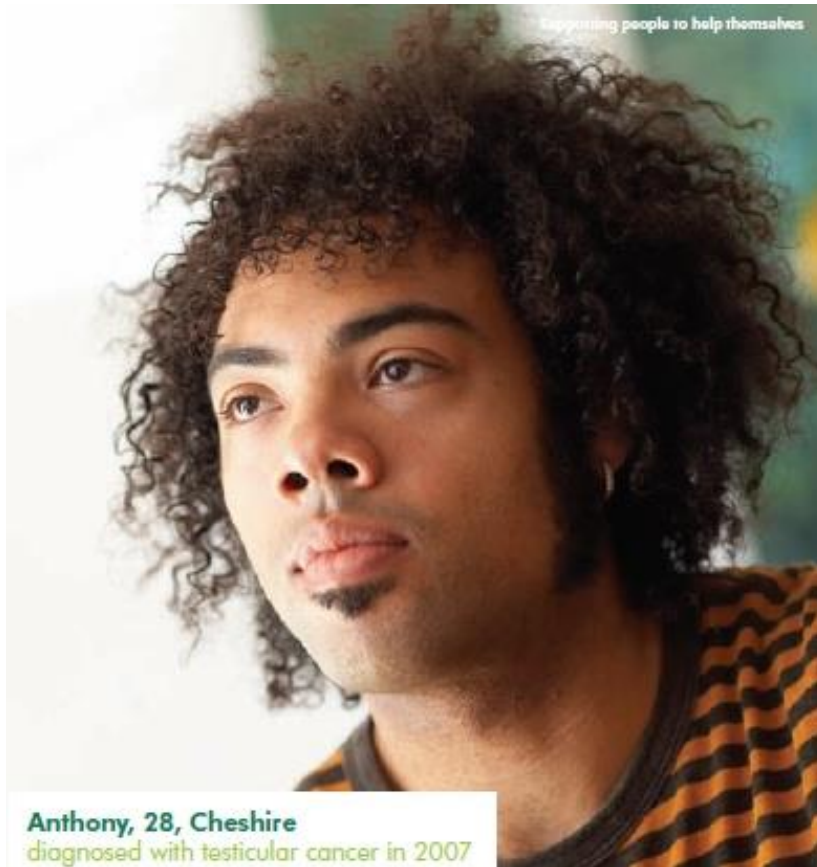
TIGER

- International randomised phase III trial
 - Conventional TIP vs 2# mobilising paclitaxel/ifosfamide followed by 3# high dose carbo-etop (TI-CE)
- Aims
 - Primary – OS
 - Secondary – PFS/toxicity (incl. mortality)/evaluate prognostic scoring system (incl. TM decline rate)/QoL/tumour biology
- Leeds
 - 7 patients screened
 - 1 in follow-up, 1 left trial, 1 declined, 4 not eligible.

Other areas of activity

- ABC trial (SWENOTECA)
 - “High-risk” stage 1 seminoma adjuvant chemo
 - 1# carboplatin vs 1# BEP
- hCG-positive seminoma
 - Use of existing datasets to evaluate if hCG elevations in seminoma impact on prognosis, and if hCG level correlates with outcome (Christoph Seidel, Denmark)
- Residual tumour resection after 1st line chemo in metastatic seminoma
 - Use of international datasets to analyse outcomes of patients with residual masses after 1st line chemo (Baciarrello, France)
- Post chemo residual tumours outside the retroperitoneum
 - Use of international datasets to analyse surgical approach, histology, prognostic impact of residual sites outside the peritoneum (Fankhauser, Switzerland)

Survivorship



‘ My cancer experience was really stressful as I’m self-employed and have had a lot of work worries. The hardest part about the cancer now is how it has affected me **mentally.**

I’m convinced that every ache or pain that I get is the cancer returning. They told me it’s been removed but it’s a constant fear.

Increasing data on late effects of treatment

- Fertility- sperm storage as routine if requiring chemotherapy
 - Second malignancy
 - Etoposide >4g and AML
 - Cisplatin and bladder cancer
 - Radiation and soft tissue sarcoma
 - Pulmonary toxicity of bleomycin
 - Cardiovascular morbidity
 - Poor bone health
 - Renal failure
 - Neuropathy- sensory and auditory
 - Testosterone depletion
 - HRQL and social difficulties
- } 3d v 5d

Community Shared Surveillance

Tumour Markers (AFP, hCG, LDH, etc)
Cancer Centre → GP/District hospital → Cancer Centre



Chase results and **upload** onto shared systems (i.e. PPM, Tracker) by **Service Coordinator**

X-ray
Cancer Centre → GP/District hospital → Cancer Centre



Chase results and **upload** onto shared systems (i.e. PPM, Tracker) by **Service Coordinator**

CT scan
Cancer Centre



CTs **run** and **uploaded** onto shared systems by local **radiology** staff. Result discussed in OPA as usual.

Self-report status
Nurse/Consultant Discussion → QTool



- **Results interpreted by local treatment team**
 - ✓ Patient recalled to Centre if problems arise
 - ✓ Patient seen in Centre once/year or when offered CT results
 - ✓ Else – Okay Letter
- **Q-Tool replaces face to face symptom self-report discussion in a standardised comprehensive manner**

Time Post-treatment

Yr 1 Yr2 Yr 3 Yr4 Yr5 Yr6 Yr7 Yr8 Yr9 Yr10

D, K, L%



A1, A2, A3, B, C, F %



E, G, H, J, M %

SJUH Local GCT based on
EAU & EGCCCG follow-up guidelines
IGCCCG risk groups
RMH Staging
NICE Guidelines

	A1	A2	A3	B	C	D	E	F	G	H	J	K	L
OPA /Tumour Markers	3m yr 1 4m yr 2 6m yr 3 =12	Same as A1 =13	Same as A2 =15	15	26	10	17	14	23	33	21	7	7
CT scans	1 in 1 st year	1 at 6m 1/year = 3	1 at 6m/year=7	4	6	3	2	4	6	7	6	2	3
CXR's	Same as OP =12	1 every 2m = 9 (1 st FBC)	1 every 4m = 6 to yr3	6	8	2	16	11	13	13	11	2	3
Years	5	5	5	5	5	3	10	5	10	10	10	3	3

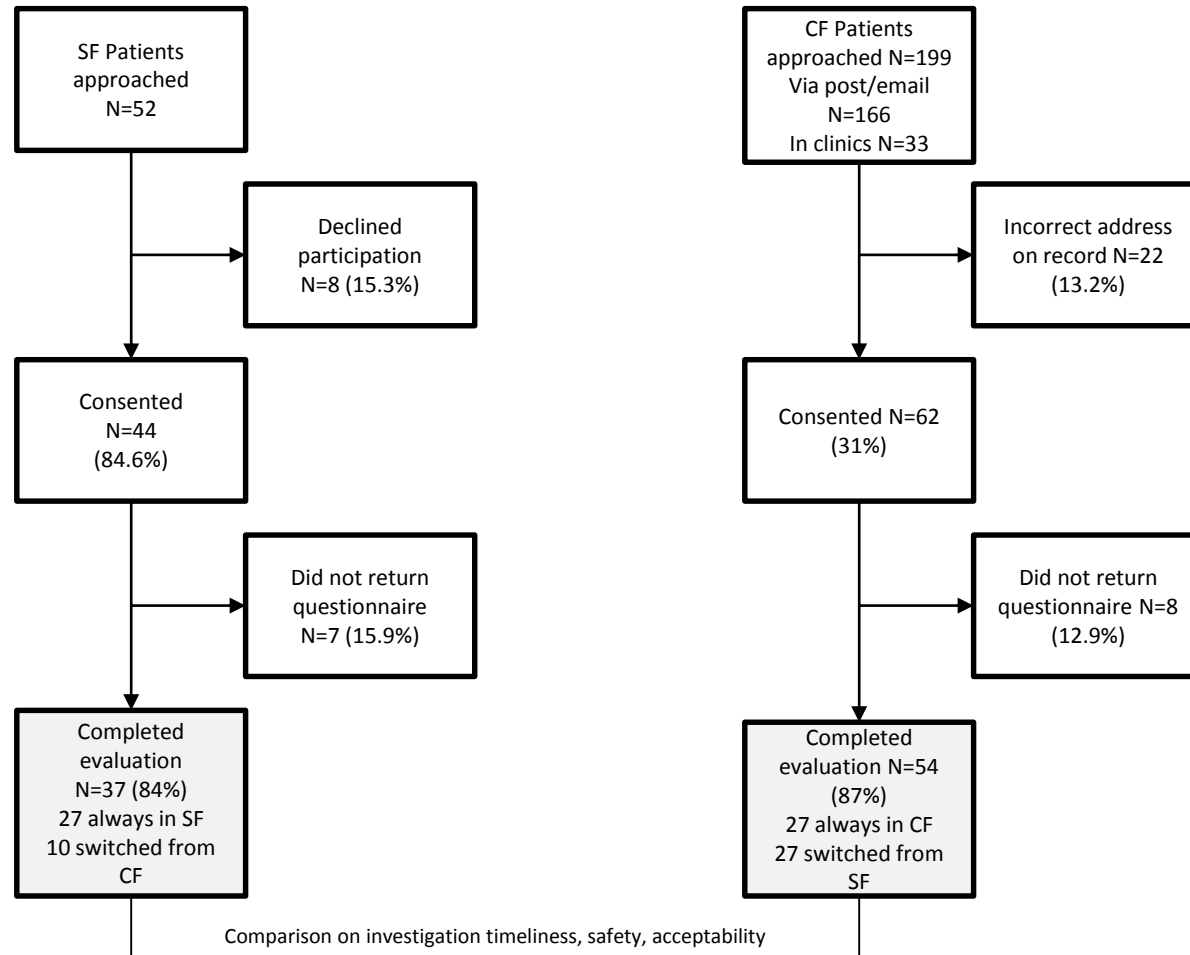
- Service safety and timeliness

- For all patients who consented to the evaluation (n=91) we extracted the timing of all investigations (clinic appointment for SF and QTool for CF, blood test, X-ray, CT) and compared it to their stratified schedule.

	Standard Follow-up (SF)	Community Follow-up (CF)	Total investigations	Mann-Whitney U, p
Total investigations up to December 2016	4356	5321	9677	p=.57
Missed investigation	529	437	966	p=.004
Investigation on time	457	844	1301	p=.03
Investigations performed outside of schedule	470	458	928	p=.03

- More investigations were missed (p=.004) and more investigations performed outside of the recommended schedule in SF than in CF (p=.03); more investigations were performed on time in CF than in SF (p=.03).

Evaluating acceptability - Recruitment



Abbreviations – SF, standard follow-up;
CF, community follow-up

- Satisfaction with information, service, and symptom management
 - Patients in CF and SF were equally satisfied ($p=.24$) and felt their concerns were addressed ($p=.21$).
 - Patients in SF perceived the responsible practitioner as more sympathetic than those in CF.
 - There were no differences on any aspects of confidence with symptom management or symptom interpretation ($p=.89$).

- Perceived costs
 - We asked all patients to estimate the costs they incurred when travelling long distances for their follow-up in the regional cancer centre, as required by the SF model.
 - Patients who chose CF instead of SF estimated that their travel to the regional centre (as opposed to having their tests in the community) was more timely, involved greater work disruption, and more out-of-pocket expenses than people who chose to remain in SF.
 - Patients in CF had to use multiple modes of transport (19.6% in CF versus 17.1% in SF), their average travel time was 96 minutes ($sd=22.31$), while for a patients in SF it was 40 minutes ($sd=23.05$), and those in CF had to take more time off work ($m=8.85$ hours, $sd=2.83$) compared to those in SF ($m=5.56$ hours, $sd=3.11$).
 - Patients in CF estimated spending on average £16.26 ($sd=6.76$) to reach their appointment when travelling to the regional treatment centre, while those in SF would spend £10.55 ($sd=17.7$).

Summary

- Background
- Concepts
- Current practice
- Recent trials/research
 - TE19, TE24, BEP111, relapsed stage 1 NSGCT, UK3
PBEP, TIGER
- Areas of activity
 - Trials, data collection
 - Survivorship
 - Community follow-up

Thank you for listening

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