Patterns of patient withdrawal from BCG treatment for bladder cancer

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PATTERNS OF PATIENT WITHDRAWAL FROM BCG TREATMENT FOR BLADDER CANCER: A RETROSPECTIVE TIME INTERVAL ANALYSIS

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PATTERNS OF PATIENT WITHDRAWAL FROM BCG TREATMENT FOR BLADDER CANCER: A RETROSPECTIVE TIME INTERVAL ANALYSIS

ABSTRACT

Research Aims

What were the patterns that have been recorded for withdrawal from treatment?

What individual factors influenced withdrawal from BCG treatment?

Literature Review

Bacillus Calmette-Guerin (BCG) vaccine was first introduced at the turn of the 19-20th century and since the 1970s has become significant in the treatment of non-muscle invasive bladder cancer (NMIBC). It is concerning to note that little is known about the patient experience of this intravesical treatment, which is particularly concerning. Despite over 50 years of clinical use, early withdrawal from treatment rates of between 32% - 86% have been reported in the literature. This study sought to estimate the rate of non-completion of BCG regime in one English National Health Service Cancer Unit and identify factors that contributed to patients' decisions to withdraw.

Methodology

A retrospective observational time interval study of a consecutive sample 234 case records of patients who underwent intravesical BCG treatment in one English National Health Service Cancer Unit, using time to event analysis. The population for this review was from a large metropolitan area in England, including a large northern town and satellites where heavy industry had dominated.

Results

The overall withdrawal rate was 211 (90%) prior to completion of induction and maintenance regime. The majority, 107 (46%) withdrew from treatment within the first

year. Age, number of side effects and symptoms, and contact with CNS were all associated with withdrawal.

Conclusions

The data has shown that age, side effects, contact details and information giving may be factors that contribute to a patient deciding whether they stay on treatment or withdraw from it.

Funding / Competing interests

None to declare

Keywords

Bladder cancer, Non-muscle invasive bladder cancer, Urothelial cancer, Bacillus Calmette-Guerin, BCG, Intravesical treatment, Early withdrawal

1. Introduction

In 2015, there were over 10,000 new cases of bladder cancer recorded in the UK only [1]. This accounts for 3% of all new cancer cases, with males being three times more likely to develop the disease than females. It is highest in people aged 85-89 years. The incidence rates for bladder cancer have been seen to be falling since the early 1990's. Reasons offered for this decline include reductions in tobacco smoking or exposure to occupational carcinogens, particularly amongst men [2]. There has also been a shift from industrial to predominantly service occupations in the UK [3]. Although tobacco smoking is still associated with around 50% of bladder cancers [4–7] and more prevalent amongst people living in deprived areas [1].

Transitional cell bladder cancer or urothelial cancer accounts for approximately 90% of all bladder cancers in the UK [1]. Non-muscle invasive, superficial or early, bladder cancer is characterised by abnormal cells localised to the lining of the bladder. Apart from recommended lifestyle changes such as smoking cessation, following a transurethral resection of bladder tumour (TURBT) intravesical treatment with Bacillus Calmette-Guerin (BCG) is considered the gold standard for preventing recurrence and disease progression in non-muscle invasive bladder cancer (NMIBC) [8]. Intravesical treatment involves instilling BCG into the bladder via a catheter. A proportion of patients, in some studies as high as 86%, fail to complete treatment [9]. This low level of concordance could have consequences in terms of disease progression and ultimately need for radical surgical interventions.

At the turn of the 19 - 20th century Albert Calmette and Camille Guerin isolated an attenuated live strain of Mycobacterium bovis bacillus, a live vaccine against

tuberculosis, known as BCG [10,11]. During a series of post mortems in 1929, Pearl noted a lower incidence of bladder cancer in patients with tuberculosis [12]. Subsequent laboratory studies demonstrated the anti-tumour effects of BCG against several malignant cell lines [13–16]. In the late seventies Morales et al. (1976) undertook a preliminary study evaluating the effects of BCG treatment on nine patients with NMIBC. Study participants were treated with intravesical BCG once a week for six-weeks, achieving a complete response rate in 7 (78%) of patients [17]. The effectiveness of this regime was later replicated in both the American South Western Oncology Group (SWOG) and the Memorial Sloan-Kettering Hospital in larger well designed control trials [18–21].

Several well designed randomised clinical trials have since compared TURBT as a single treatment, against a TURBT followed by BCG [18,22–24]. Other randomised trials and meta-analyses compared various combinations of TURBT, chemotherapy and BCG regimes [9,25–30]. These studies demonstrated significant reductions in NMIBC recurrence rates of up to 57% in patients treated with BCG, compared to rates of up to 32% when treated with TURBT alone, or with chemotherapy.

Globally sub strains of BCG such as Pasteur, TICE, Armand-Frappier, Glaxo, Connaught and others are in use [31] creating an absence of clarity regarding optimum strain or dose, as well as different regimes and doses [30–32]. A consensus statement concluded that regimens other than SWOG have not shown the same reliability [33]. Only one study compared two strains head to head [34]. They compared the Connaught and TICE strains and showed a statistically significant difference ($p<0.002$) in five-year recurrence-free survival for Connaught (75%) over TICE (46%) treated patients.

At present there remains no overwhelming evidence indicating the optimal efficacy for the most appropriate induction and maintenance regime. This is illustrated in table 1. Induction BCG was first introduced by Morales et al. and is normally given using a six-weekly regime. Results from the SWOG 8507 trial[9] and European Organisation for Research and Treatment of Cancer (EORTC) 30911 trial [27], recommend an induction regimen of weekly instillations for six weeks, followed by a maintenance schedule of weekly instillations for three weeks at months 3, 6, 12, 18, 24, 30, and 36 for a total of 27 instillations for three years. Maintenance for three years was affirmed by a subsequent EORTC trial [35]. This regimen has now been recommended by the American Urological Association (AUA) and the European Association of Urology (EAU) as well as in local guidelines [36–39]. The EAU guidance recommends that at least one year of maintenance treatment is required to gain superior outcomes over Mitomycin (MMC) treatment [8]. The absence of an established optimal induction and maintenance schedule may be as a consequence of the wide variations in regimes in current use [40–42]. Moreover, the original and subsequent trial design irrespective of minor variations have all adopted an induction and maintenance model yet report high levels of attrition. Clinical practice has adopted the same model.

This paper presents the results of a study investigating the clinical experiences of patients receiving BCG treatment, using retrospective time interval analysis from case notes. This was the first phase in a larger mixed methods study exploring the reasons why patients withdrew from BCG treatment early.

Insert Table 1

From the literature the following question emerged which the time interval analysis sought to answer: what were the patterns that have been recorded for withdrawal from treatment? and what individual factors influenced withdrawal from BCG treatment?

2. Methods

A retrospective time interval analysis was undertaken.

3.1. Population

The study was undertaken in a cancer centre based in a large National Health Service Hospital Trust serving a large metropolitan area in Northern England. The area had traditionally been characterised by heavy industries such as coal mining and textiles, but, latterly as chemical manufacturing. One in six of the local population are aged 65 years or over [43].

This population is diverse and undergoing change. Partly in consequence of easing of European borders, allowing easier movement of working age adults seeking employment. The ethnic make-up of the white population in this area has changed, growing from 3.3% in 2001 to 7.2% in 2011. This is due to an influx of a largely Eastern European population e.g. Polish. The remainder of the population are of a black and ethnic minority population predominately of Indian sub-continent heritage. The district is the 67th out of 326 districts, most deprived districts in England, with 12.5% living in areas rated in the 10% most deprived. Life expectancy of local males is 77 years and 81 years for females. Cancer incidence and mortality in this district is higher than other manufacturing towns in England [43].

3.2. Sample

Patients aged over 18 years with a histological diagnosis of NMIBC were included in this analysis. They had a grading of grade 3 bladder cancer with one, or a combination of, the following stages: Ta; T1; or carcinoma in situ (CIS). Commencing BCG treatment within the 12 months prior to the commencement of this study and had withdrawn from treatment. Patients who had progression or recurrence of bladder cancer and were not receiving BCG treatment were excluded.

A sample of 234 sets of patient case notes (1st January 2004 to 31st December 2011), fitted the inclusion criteria, which were included in this study. This was considered representative of the population [44]. The characteristics of the sample are described in table 2.

Ethical approval was obtained from local research ethics committee (12/YH/0481) and the university where study was conducted. The researchers were not involved in the administration of intravesical BCG treatment or in the management of any of the healthcare professionals (HCPs) within the units where treatment was given.

3. Data Collection

A data extraction tool was designed and pilot tested by the researcher. Only the researcher conducted the data extraction. The clinical data relating to BCG treatment received by patients gathered also illustrated the 'natural history' of BCG treatment and identified trends concerning symptomology e.g. timing of symptom occurrence

and decisions recorded for treatment withdrawal. The tool was tested on a sample selection of case notes (n=10) and adjustments made to refine the tool.

During the study, the NHS Trust moved towards being 'paper-light', hampering healthcare records collection of the data in three ways. Firstly, for those patients who still had paper notes, locating the notes and in many cases retrieving from storage took multiple requests and time delays. Secondly, paper notes already scanned into the electronic data management system posed different challenges. Such as delays caused by the time taken to scan documents and upload them and two the volume of screens of scanned documents per case note, as many as 500, which needed to be reviewed to extract relevant data. Thirdly, some prescription cards were held by each unit and not with the case notes and these needed to be examined separately.

4. Data Analysis

Once extraction was completed, all data were transferred into IBM SPSS version 20 for Windows. Data were then analysed using the Kaplan-Meier method. This allows estimation of withdrawal over time, even when patients remain the study for different lengths of time [45]. Cox regression modelling was used to interrogate withdrawal data, allowing treatment effects to be isolated from influences of other variables [45,46].

5. Results

There appears to be several significant factors or patterns that arise from the case-note analysis, which indicates a withdrawal rate of 90% and that the majority withdraw, 107 (46%), from treatment within the first year. The most commonly recorded side effects involved a treatment related pain dimension e.g. pain, cystitis, sore genitalia.

Urinary side effects such as frequency and urgency were also commonly reported. Age was also an important factor, as those who were 70 years or over were more likely to withdraw from treatment.

The findings are presented in five sections: study population and characteristics; patterns of withdrawal; factors influencing withdrawal; decisions for withdrawal; and Likelihood of withdrawal. The term 'time to event' for this study is defined as being the time taken to the event of interest namely withdrawal from BCG treatment.

6.1. Study population and characteristics

Most participants were aged over 70 years, 140 (61%), and the majority were male, 188 (80%). Only 23 (10%) of the sample population completed the full three-year treatment regimen lower than the 16% identified in the South Western Oncology Group (SWOG) trial [9].

Table. 2.

6.2. Patterns of withdrawal

The time to event analysis looked at protocol deviation by charting each instillation and the timing between instillations. Thereby, looking for patterns or areas of variability. These variations can be seen in Figures 1-7, which illustrate a number of curves. The significance of the divergent patterns is addressed with the log rank test, this showed that there was correlation with age and that the chance of an event occurring e.g. having a side effect, rises with age. The data also shows that those who

experienced one or more side effects were more likely to withdraw from treatment early, 71 (53%) withdrawing within 35 days of starting treatment.

Fig. 1 shows when each participant completed treatment. The largest withdrawal occurs prior to the one-year mark. From these data, 36 (15%), of patients extended treatment beyond the three-year treatment protocol. This may be due to delays in the instillations, which then offset other instillations, being given later than planned, or the possibility that the patient had been lost to follow up and then continued when found.

Fig. 1.

Figure 2 shows that by concentrating the curve to 36 months, representing three years of treatment, it shows that patients are more likely to withdraw from treatment within the first 365 days (one year). On interrogation of those 107 (46%) of patients that withdrew by 12 months, one year), of treatment a greater proportion, 39 (36%), withdrew within the first 42 days (see Figure 3).

Fig. 2.

Fig. 3.

6.3. Factors influencing withdrawal

Fig. 4 shows comparison of time to withdrawal from treatment by age. Participants aged over 70 years have a lower time to event probability than those aged 69 years or younger. Log rank statistic 17.34 (p=0.001). Age in this population was a significant

factor in withdrawal from treatment. Likewise, those who experienced one or more side effect associated with BCG treatment (log rank statistic 7.27 (p=0.007)) were more likely to withdraw from treatment (See Figure 5).

Fig. 4.

Fig. 5.

As contact with a clinical nurse specialist (CNS) is one of the standards recommended in cancer standards [47] compliance with this requirement was extracted from the case notes. Figure. 6 shows if a record of a patient receiving CNS contact information whereas Figure 7 illustrates receiving information about the treatment from a CNS. From these data it appears that receipt of contact details of a CNS (log rank statistic 4.46; p= 0.035) or receiving information about the procedure and side effects (log rank statistic 23.052) (p<0.001) was more likely to be associated with withdrawal from treatment.

Fig. 6.

Fig. 7.

6.4. Decisions for withdrawal

The reasons recording decisions to withdraw from treatment were categorised into five broad areas: Side effects, patient/carer, hospital related, disease related, or other reasons. The largest single grouping was treatment associated side effects (see Figures 8-10). The time to event analysis revealed, what appeared to be a natural age

group split. Participants were grouped 69 years or younger and those aged 70 years or over. When categorised by age, there was little difference in the reasons given for withdrawing from treatment. Documented side effects appeared to be a major contributor to the decision to withdraw with two thirds, 156 (67%) of participants, with at least one side effect recorded.

Fig. 8.

Fig. 9.

Fig. 10.

Side effects experienced are shown in Figs. 11-13. The majority of reported local symptoms were urinary including frequency of urination (n=41, 39%), haematuria (n= 33, 31%), cystitis (n= 29, 28%) etc. Generalised pain which was not localised (n=22, 31%) was reported as being the most common systemic side effect. Unknown reactions (where a reaction was recorded, but no details given) (n=18, 39%) and difficulty in catheterisation were the most common other side effects reported.

Fig. 11.

Fig. 12.

Fig. 13.

6.5. Likelihood of withdrawal

In the Cox regression modelling that was undertaken, all variables were considered for inclusion were screened. Those which did not appear important individually or comprised categories with frequencies too low to analyse were excluded. The remaining variables were then analysed in combination to identify any emerging patterns. This method assumes that covariates are multiplicatively related to the hazard e.g. experiencing a side effects raises the likelihood of withdrawal [48]. Variables included were those that: had a low p-value (≤0.05) at 'screening stage' indicating the likelihood he variable occurring by chance was less than 5%; were clinically important (side effects recorded as reason for patient withdrawal); or those selected through automated selection routine which the proportionality of the hazards assumption was validated. The variables that appear significant are presented in Table 3.

Table 3

6. Discussion

A major cause for early withdrawal was side effects, although age was associated with higher withdrawal rates. The reasons given for withdrawal from treatment were the same, or similar, in all age groups except for side effects. It was found that 31 (40%) of participants aged 69 years or younger side effects were cited as a reason for withdrawing from treatment, a higher proportion than the 44 (33%) of participants aged 70 years or older. These results are in contrast to Heiner and Terris's study, where the number of patients who experienced side effects aged 70 years or over were higher than in patients 69 years or younger respectively, 56% vs. 40% [49]. Although reported as significant ($p<0.00001$), the study sample was small, 58 participants, with only 22

experiencing side effects suggesting it was underpowered. The number of participants who experienced side effects were greater 156 participants in this study; with 92 (59%) aged over 70 years experiencing at least one side effect. An alternate explanation could relate the strains and/or doses of BCG administered. In the absence of consistent practice regarding optimum strain or dose [30–32], this inconsistency may explain varying levels of withdrawal. Similarly, differences in number and severity of side effects experienced may strain or dose dependent. Within this analysis all patients received the same strain of BCG.

Some suggest that interstitial BCG treatment needs to be administered cautiously in patients 70 years or older and only after careful consideration due to poor reserves that these patients may have to cope with the treatment [50]. This is predicated on the basis that side effects from BCG treatment would not be as well tolerated in elderly patients and may become problematic in terms of adherence. This pattern was seen in this study population. Whether this was a consequence of poor toleration or the treatment burden was in excess of physical reserves and/or co-morbidity was not assessed.

The analysis supports the given view that side effects experienced affects attrition. Patients who are well prepared about what to expect, such as those involved in clinical trials, may be better prepared when encountering side effects; in effect they cope by normalising the abnormal. The results of this study suggest that those patients who are given more information, were more likely to withdraw.

A surprising feature of this study and should be treated cautiously, was contact with a CNS may not contribute to keeping patients on treatment for longer. The reasons for this finding are unknown but warrants further investigation, particularly, as in other cancer site specific studies CNS input seems to improve outcomes [51]. However, this could be related to poor record keeping, in that those case records where details of the CNS were provided, patients were more likely to withdraw from treatment early, than those whose records showed they only received written information.

The time to event analysis of withdraw from treatment revealed a natural age group split with patients 69 years and under more likely to tolerate and continue to receive BCG for nine months longer than those aged 70 years and above. Further, 63% of the population aged above 70 years old in this study were more likely to withdraw reasons for attrition were similar. Not only was there a correlation between age and the chance of the event occurring, but the modelling highlighted that the percentage chance of the event occurring rises with age.

During data extraction three patient records documented the rationale for treatment cessation as 'advanced age'. This does question whether an adequate assessment was completed prior to treatment. The higher number of participants aged 70 years or greater in the study probably reflects the local population, with increasing life expectancy and effects of exposure to dye, printing, iron, industrial painting, gas and tar industries during employment only presenting long after exposure [8]. This generation may not have benefitted from the impact of health and safety legislation in the work place or recent anti-smoking campaigns [52].

There is clear evidence of side effects associated with BCG use [9,26,27]. Reportedly between 20% and 80% of patients experience mild to severe local or systematic, side effects [53–55]. The reported studies do not detail the effect that side effects have on the patient.

This study discovered that 67% of patients who experienced one or more side effect, such as cystitis or incontinence, were more likely to withdraw early. The analysis showed that 55% of participants withdrew within the first year. Of these, 39% withdrew within 42 days of treatment commencing, hence failing to complete the induction phase of the treatment (the initial six instillations). Data regarding subsequent treatment(s) if any or long terms outcomes was not extracted and therefore any assumptions about whether patients were being put at risk of recurrence through early withdrawal are unknown. That said poor selection for BCG may have delayed alternative interventions.

Nearly half of the of participants (45%) reported at least one local side effect e.g. urinary frequency; with 30% reporting at least one systemic side effect; and 20% reporting at least one other side effect or treatment related complication e.g. difficulty in catheterisation. The most common local side effect reported was cystitis and according to Lamm et al. experienced in around 80% receiving BCG [53]. In contrast, in this study, cystitis was recorded in only 28% of cases (Fig. 11). The most commonly recorded local side effect in was urinary frequency in 39% of cases. A possible reason for differences in symptom incidence may relate to how side effects were reported and/or recorded in case notes. Cystitis involves both frequency and pain, or a burning sensation, when urinating [56]. As the instillation of BCG is largely a nurse led service,

in that the CNS counsels the patient, instils the BCG, records in the case notes and discharges the patient from the unit. They remain the main contact for the patient when they go home, therefore, this impacts onto any findings. The CNS may have recorded these side effects separately, or one in preference to both, or interpreted the symptoms and given a different descriptor thereby skewing the actual number of participants who did have the side effect of cystitis.

It is unclear in the literature when side effects occur. Some authors indicate that side effects can occur during the induction phase of the treatment, however they do not suggest that there is a cumulative effect from the BCG instillations when the symptoms appear during maintenance [49,57–59]. In this study there were 53% reports of side effects experienced within 35 days of starting treatment indeed for some these started within the first week of treatment commencing.

A limitation of all studies interrogating clinically available data, is the quality of the original record keeping and accuracy of data extraction. As this study used paper-based notes (patient records and prescription charts) this may have introduced greater levels of inaccuracy as clinician preference and style may influence what is recorded. Unlike electronic records which force data entry arguably increasing reliability [60]. Although some suggest the problem of data accuracy has more to do with why it is collected namely research versus clinical purposes. The introduction of electronic health records may have increased the tendency for bad data recording rather than greater accuracy [61].

7. Conclusions

From this retrospective time interval analysis of clinical data withdrawal rates from BCG treatment were higher than those published in the literature. The patterns that emerged associated with age and experience of side effects appeared to significantly affect the decision making regarding early withdrawal from treatment. The majority of attrition appears to occur within the first year of treatment, and indeed a sizable group prior to completing induction. Possibly the most surprising finding was that clinical nurse contact and information provision seemed to exacerbate early withdrawal. This may be an anomaly associated with a real-world nurse led service design. What is clear is that further research is required to fully understand these results, but they contribute real world insight into the experience of a 'gold standard' treatment.

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Fig. 1: Early withdrawal or course completion overall view

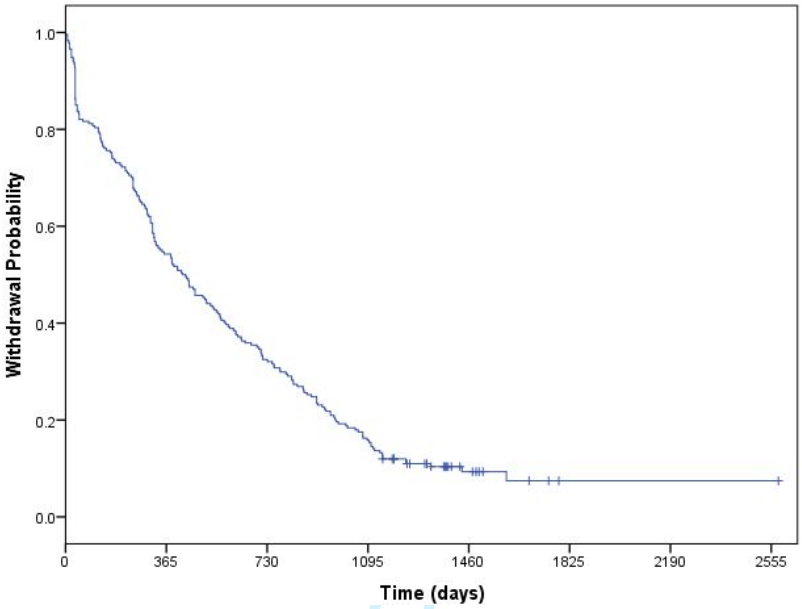

Fig. 2: Early withdrawal or completed 36 months (three years) of treatment

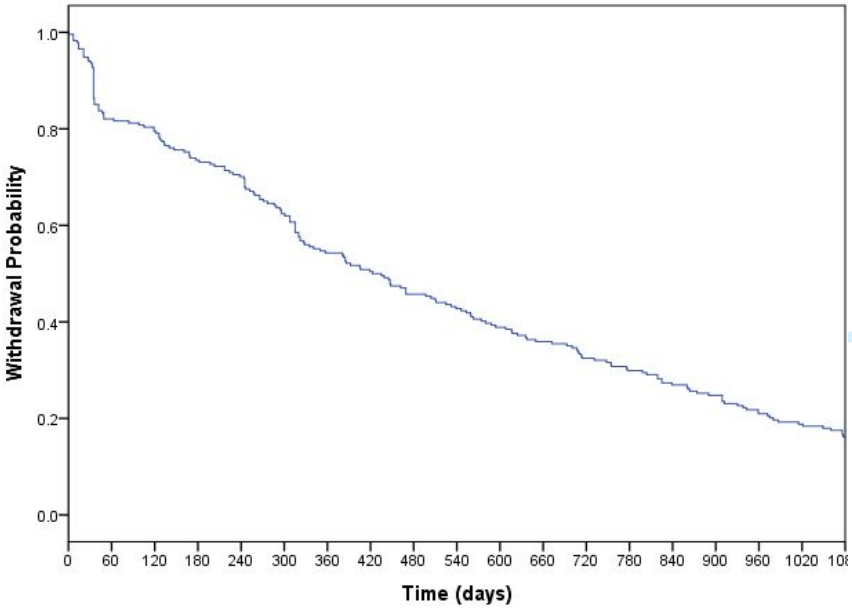

Fig. 3: Early withdrawal or completed 12 months (one year) of treatment

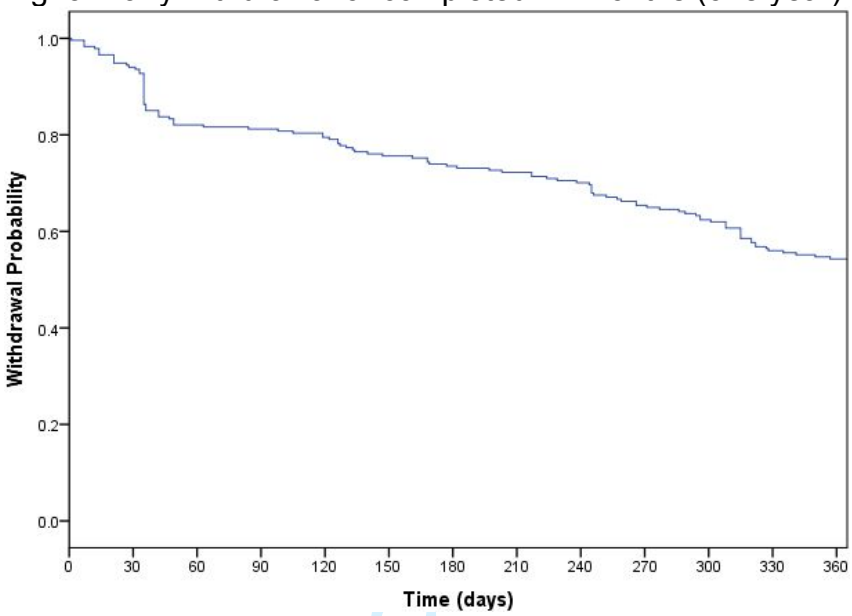

Fig. 4: Treatment withdrawal by age group

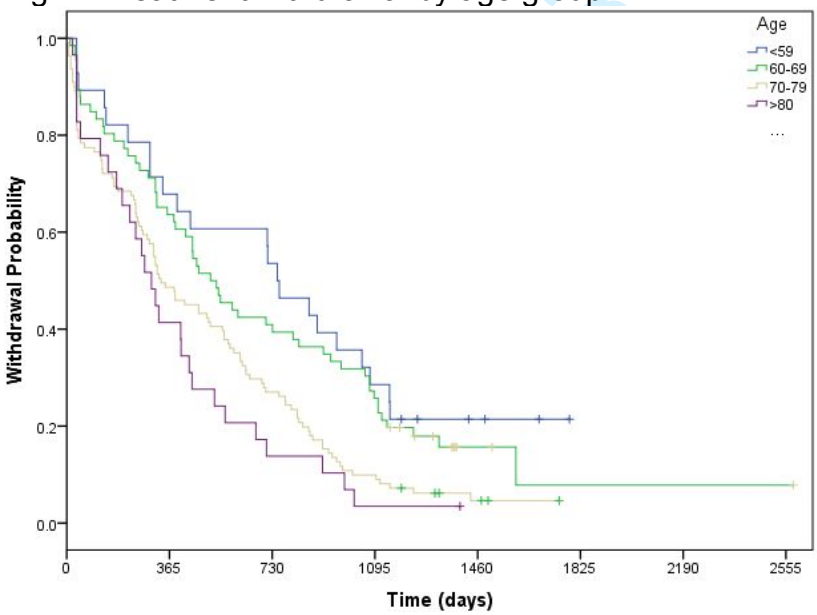

Fig. 5: Early withdrawal through side effects

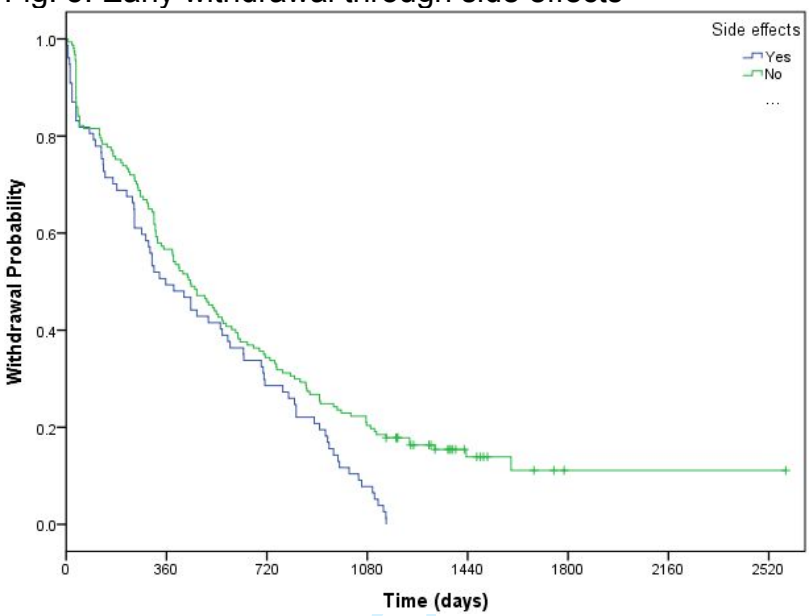

Fig. 6: CNS contact details given to a patient

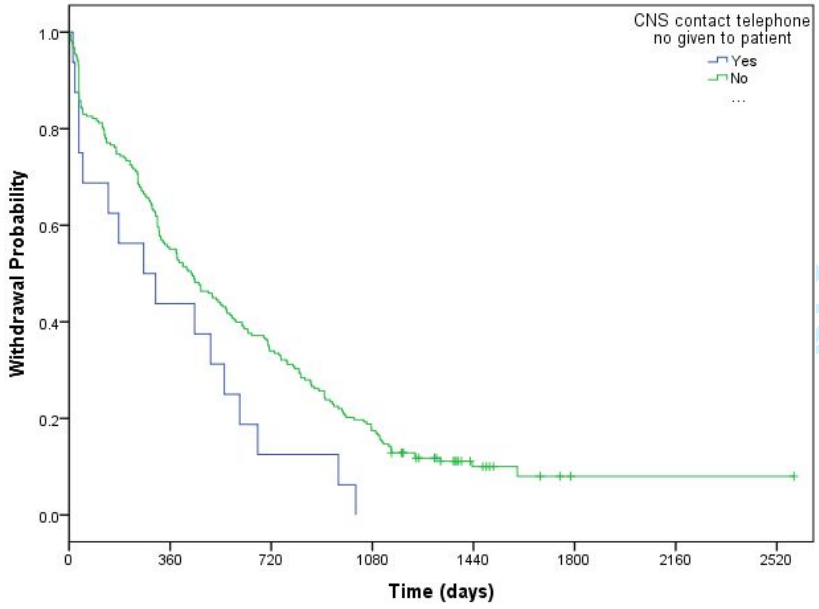

Fig. 7: Written information given to a patient

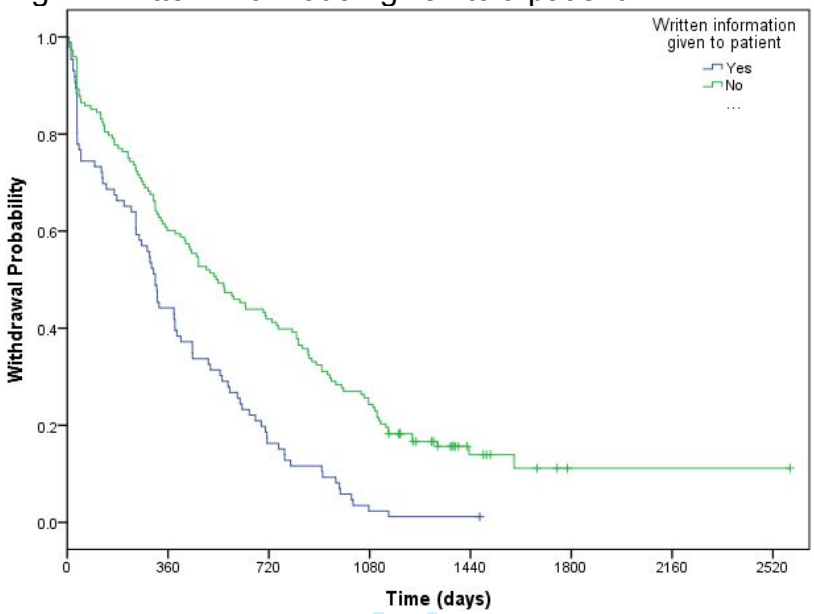

Fig. 8: Reasons given for withdrawal

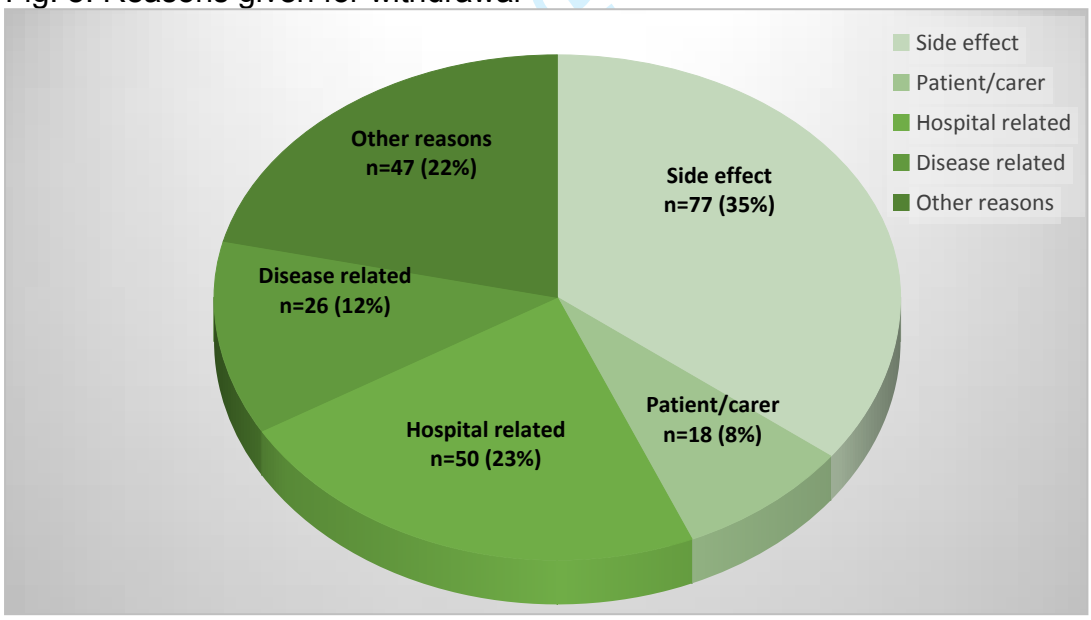

Fig. 9: Comparison of withdrawal reasons by age

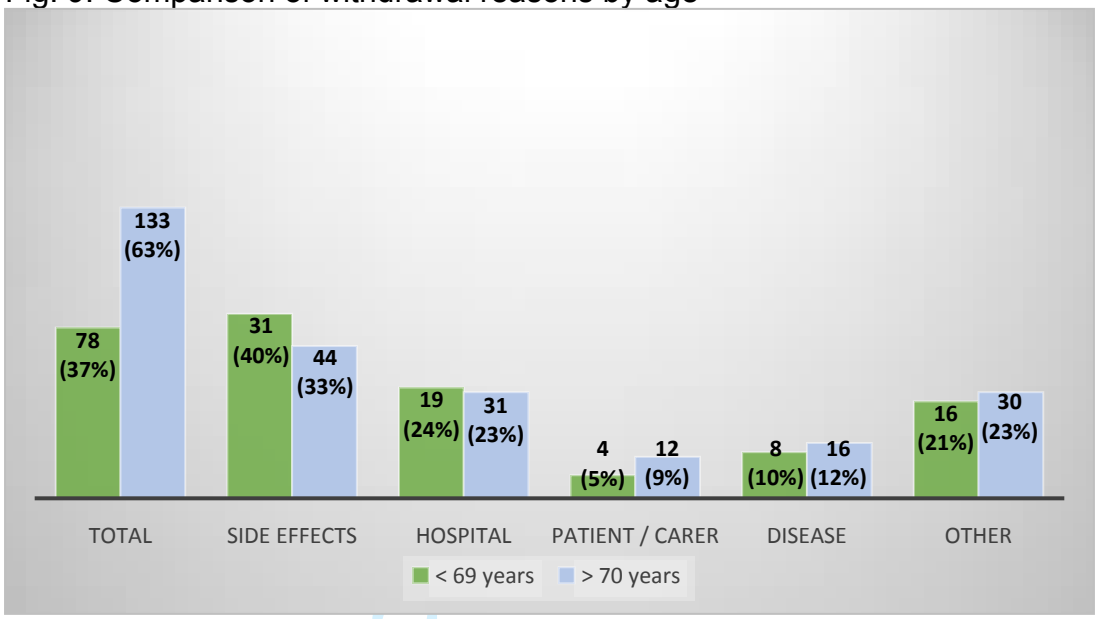

Fig. 10: Recorded number of side effects from case notes

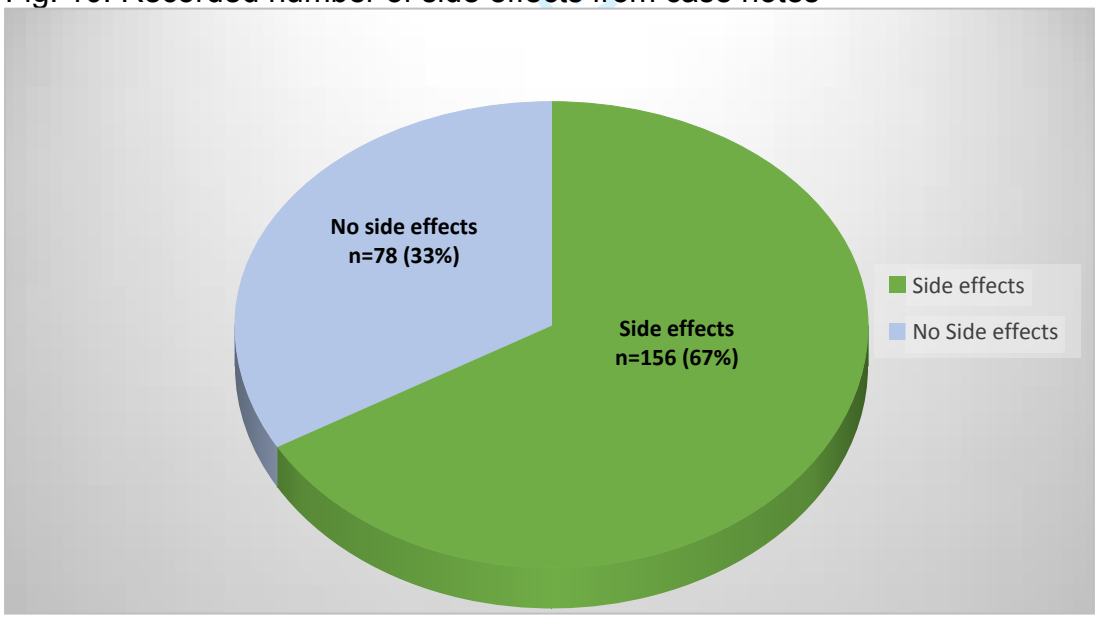

Fig. 11: Reported local side effects

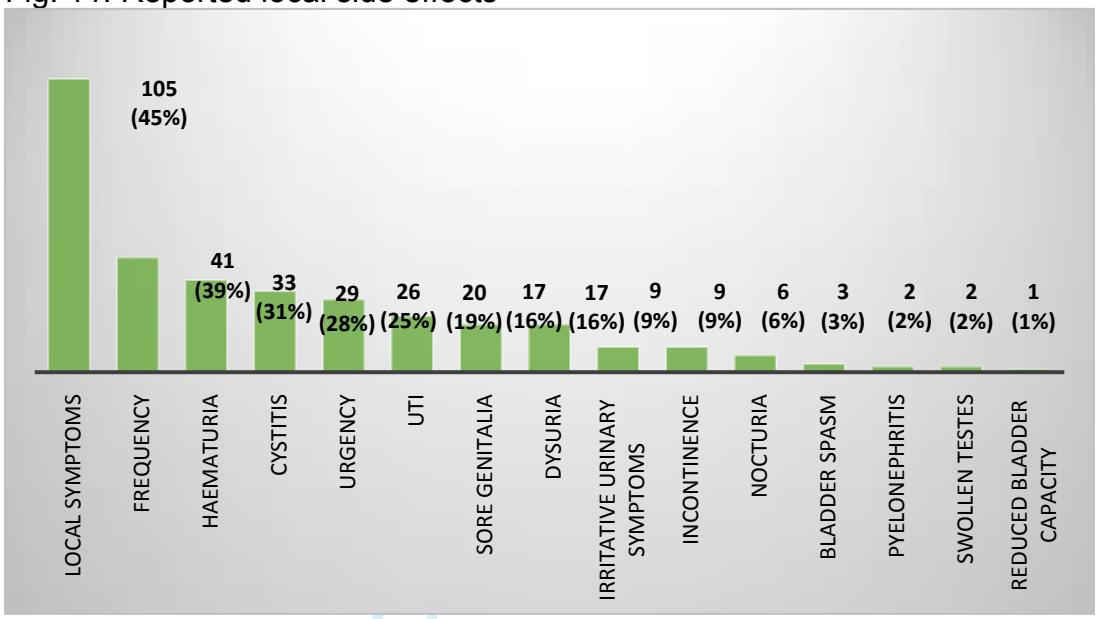

Fig. 12: Reported systemic side effects

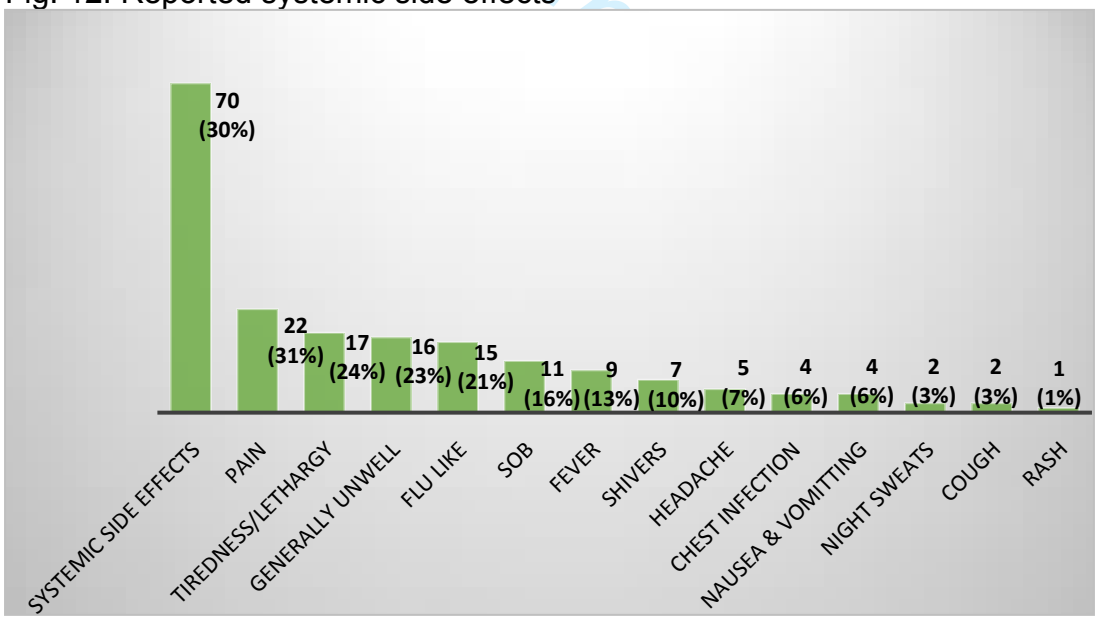

Fig. 13: Reported 'other' side effects

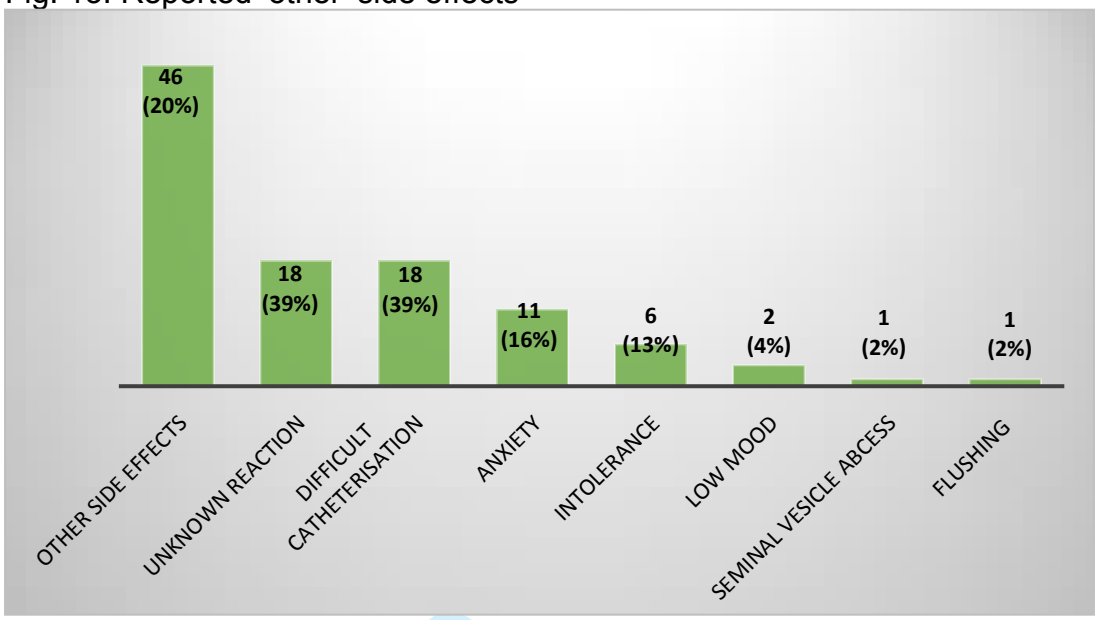

Table 1: Studies showing BCG dose, strain and treatment regime

Study	Dose / Strain	Induction Regime	Maintenance Regime	Percutaneous BCG
Morales et al. (1976)	120mg / Armand Frappier	Weekly for 6 weeks	No	Yes
Herr et al. (1983)	120mg / Armand Frappier	Weekly for 6 weeks	No	Yes
Badalament et al. (1987)	120mg / Armand Frappier	Weekly for 6 weeks	Monthly for 2 years	No
Hudson et al. (1987)	120mg / Pasteur	No	1 instillation every 3 months for 2 years	No
Agrawal et al. (2007)	40,80,120mg / Modified Danish 1331	Weekly for 6 weeks	Monthly for 1 year	No
Ali-el-dein et al. (1999)	150mg / Strain not given	Weekly for 6 weeks	Monthly for 10 months	No
Andius & Holmang (2004)	Dose not stated / Modified Danish 1331 & TICE	Weekly for 6 weeks	Monthly for 2 years	No
Orihuela et al. (1987)	120mg / Pasteur	Weekly for 6 weeks	No	Yes
Lamm et al. (1995)	50 mg / TICE	Weekly for 6 weeks	Monthly for 1 year	No
Bohle et al. (1996)	150mg / Connaught	Weekly for 6 weeks	No	No
Krege et al. (1996)	120mg / Connaught	Weekly for 6 weeks	Monthly for 4 months	No
Taniguchi et al. (1999)	80mg / Tokyo 172	Weekly for 6 weeks	No	No
Witjes et al. (1996)	$5x10^8$ / TICE & RIVM	Weekly for 6 weeks	No	No
Witjes et al. (1998)	40mg of Mitomycin C then BCG	Weekly for 6 weeks	No	No
Lamm et al. (2000)	81mg / Connaught	Weekly for 6 weeks	Weekly for 3 weeks at months 3, 6, 12, 18, 24, 30 and 36	Yes
Saint et al. (2001)	81mg / Connaught	Weekly for 6 weeks	Weekly for 3 weeks at months 3, 6, 12, 18, 24, 30 and 36	No
van der Meijden et al. (2001)	$5x10^8$ / TICE	Weekly for 6 weeks	Weekly for 3 weeks at months 3, 6, 12, 18, 24, 30 and 36	No

Fonseca et al. (2002)	40mg / Moreau-Rio de Janeiro	6 instillations – not clear over what time period	6 instillations each 15 days	No
van der Meijden et al. (2003)	$5x10^8$ / TICE	Weekly for 6 weeks	Weekly for 3 weeks at months 3, 6, 12, 18, 24, 30 and 36	No
De Reijke et al. (2005)	81mg / Connaught	Weekly for 6 weeks	Weekly for 3 weeks at months 3, 6, 12, 18, 24, 30 and 36	No
Gunlusoy et al. (2005)	120mg / Pasteur	Weekly for 6 weeks	No	No
Decobert et al. (2008)	120mg / Pacis Shire	Weekly for 6 weeks	Weekly for 3 weeks at months 3, 6, 12, 18, 24, 30 and 36	No
Jarvinen et al. (2009)	75mg / Pasteur	Weekly for 5 weeks	Monthly for 2 years	No
Duchek et al. (2010)	Dose not stated / TICE	Weekly for 6 weeks	Weekly for 3 weeks at months 3, 6, 12, 18, 24, 30 and 36	No
Hinotsu et al. (2010)	81mg / Connaught	Weekly for 6 weeks	Weekly for 3 weeks at months 3, 6, 12 and 18	No
Sylvester et al. (2010)	$5x10^8$ / TICE	Weekly for 6 weeks	Weekly for 3 weeks at months 3, 6, 12, 18, 24, 30 and 36	No
Oddens et al. (2014)	$5x10^8$ / TICE	Weekly for 6 weeks	Weekly for 3 weeks at months 3, 6, 12, 18, 24, 30 and 36; or	No

			Weekly for 3 weeks at months 3, 6 and 12	
Rentsch et al. (2014)	6.6–19.2 108 CFU / Connaught 2–8 108 CFU / Tice	Weekly for 6 weeks	No	No

Table 2: The age distribution and gender of the population

Characteristic	n	%
Age (years)		
<59	28	(12)
60-69	66	(28)
70-79	111	(48)
>80	29	(13)
Mean age	71	
Standard deviation	8.54	
Gender		
Male	188	(80)
Female	46	(20)
Course Complete		
Yes	23	(10)
No	211	(90)

Table 3: Cox regression model parameters

Variable	p - value	Hazard Ratio (HR)	95.0% CI for HR	
			Lower	Upper
Age				
>80 (reference)				
<59	0.007	0.427	0.231	0.789
60-69	0.018	0.558	0.345	0.903
70-79	0.241	0.765	0.490	1.197
Patients withdrawn due to:				
No side effects or side effects (reference)				
Side effects or side effects	<0.001	5.443	3.481	8.510
No patient or carer decisions (reference)				
Patient or carer decisions	0.002	2.379	1.368	4.134
No hospital events (reference)				
Hospital events	<0.001	2.898	1.736	4.837
No miscellaneous reasons (reference)				
Miscellaneous reasons	<0.001	7.057	4.308	11.561
Patients who received:				
No information (reference)				
Information	<0.001	1.857	1.322	2.610
Patients who experienced:				
No local side effects (reference)				
Local side effects	0.026	0.695	0.505	0.958