SPINAL TUBERCULOSIS
A DUTCH PERSPECTIVE
SPECIAL REFERENCE TO SURGERY

RIJKSUNIVERSITEIT GRONINGEN

SPINAL TUBERCULOSIS, A DUTCH PERSPECTIVE
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CONTENTS

CHAPTER 1
INTRODUCTION AND AIMS

A brief, general introduction of tuberculosis (TB) will provide some background for a better understanding of this thesis on tuberculosis of the spine. TB is a fascinating and ancient infectious disease caused by the *Mycobacterium tuberculosis*. The earliest human remains show deformities caused by TB. This has been confirmed by skeletal DNA[1]. TB has always been present throughout history. Incidence in developed countries has steadily declined thanks to better hygiene and improved socio-economic conditions. Despite effective medication introduced in the 1950s, TB still is present today. In the early 1990s there was a resurgence of TB worldwide, especially due to the increase of human immunodeficiency virus (HIV) and the acquired immunodeficiency syndrome (AIDS)[2-5]. It is interesting that people with HIV/AIDS turned out to have an increased risk of developing extra-pulmonary forms of TB, including spinal TB[6-10]. In 2003 there were 8.8 million new cases of TB worldwide, 674,000 of which were infected with HIV. In that year the incidence rate was falling or stable in most regions of the world, but growing at 1.0% per year globally because of the African Region, where incidence has been rising more quickly in countries with higher HIV prevalence rates. In Eastern Europe the incidence rate increased during the 1990s, peaked around 2001, and has since fallen. The rise in global incidence is decelerating because HIV epidemics are slowing down in Africa, but it is unclear when the global incidence rate will begin to decline[11]. Today, approximately two million people die from TB each year worldwide[12].

The Netherlands is one of the countries that have approached the elimination phase of tuberculosis[13]. After a continuous drop to an all-time low in the Netherlands of 1192 patients in 1987, incidence rates increased to a stable number of about 1500 between 1995 and 2001. Since then, numbers decreased to 1300 in 2003. The National Tuberculosis Register of the KNCV Tuberculosis Association showed an increase in bone and joint TB (BJTB) in recent years despite the more or less stable overall incidence[14].

Transmission of TB occurs through air droplets that enter the body via the airways if someone coughs with 'open tuberculosis' (contagious form). In most people the bacilli get eliminated, in others they become dormant, and 10% develop the disease. People usually develop pulmonary TB, 15% get an extra-pulmonary tuberculous lesion, and of this latter group 10% is BJTB. Four percent of all tuberculosis patients develop BJTB, half of which is located in the spine[14,15].

Anamnesis and past medical history can be very helpful in diagnosing TB. The risk of developing tuberculosis increases manifold if a patient belongs to a risk factor group that includes inmates and staff of correctional facilities, residents and staff of nursing homes, homeless people, health care workers, prostitutes, substance

abusers, immigrants from endemic areas, immunocompromised people, and people with a past history of TB[10]. Contact with contagious TB-patients is a risk factor as well, leading to extensive contact investigations. Work-up often comprises a Mantoux test and a chest radiograph. Laboratory parameters in general are not specific. The diagnosis of spinal TB can be difficult to establish. The differential diagnosis comprises septic spondylodiscitis, metastasis and primary bone tumours. The characteristic radiological image of an active tuberculous spinal lesion is that of affected or collapsed vertebral bodies on both sides of a destroyed disc and abscess formation[16-19]. CT and MRI can accurately assess formation and extent of abscesses, as well as narrowing of the spinal canal and spinal cord compression. Because of the relatively slow onset of TB, large abscesses can be seen with huge bony destruction before clinical symptoms are prevalent[19]. Biopsy material from the lesion is often needed to confirm the tuberculous origin with histology and cultures. The tissue should be sent dry or in a wet gauze, not in preservation fluid like formaldehyde that kills the *M. tuberculosis*.

Treatment of tuberculosis in the old days, before the introduction of chemotherapy in the 1950s, was rest and fresh clean air, preferably in sanatoria. Nowadays chemotherapy is the mainstay of treatment, given for a period of six months or longer (9-18 months)[10;20-22]. It usually consists of a standard combination of 6 months Isoniazid (ISO) and Rifampicin (RIF), and 2 months of Pyrazinamide (PYR). If the resistance pattern is unknown, a fourth drug is added: Ethambutol (ETH). Compliance is of the utmost importance to prevent the emergence of resistant strains of *M. tuberculosis*. DOTS is originally the abbreviation for direct observed treatment strategy, where medication is taken under supervision of medical staff. Today it stands for the internationally recommended strategy for controlling TB, consisting of five elements: government commitment to TB control, diagnosis through bacteriology and an effective lab network, standardised short-course chemotherapy with full patient support throughout treatment, uninterrupted supply of quality-assured drugs, and recording and reporting to measure patient and program outcomes[11].

Spinal TB demands a multidisciplinary approach in both diagnosis and treatment. Chest physicians, tuberculosis experts, community health workers, radiologists, microbiologists, pathologists, neurosurgeons and orthopaedic surgeons need to collaborate closely to provide optimal care. Spinal TB is a very serious form of the disease because of the unique orthopaedic and neurological problems it poses. TB demineralises and destroys the bone, causing collapse. Even compression of the spinal cord can occur by protruding bone, abscess formation around the spinal cord and reactive edema[15;23-28]. Large psoas abscesses may also be generated by continuous spread of the tuberculous lesions from the spine.

Chemotherapy is clearly the most important element of TB treatment, but

because of the difficult problems encountered in the spinal form of TB, like kyphosis and paraplegia, there may be indications for surgery as well. The role of the surgeon in spinal TB has been debated in the literature since the 1960s. Konstam advocated conservative treatment without surgery because of the good results achieved in Nigeria, and Hodgson in Hong Kong performed radical surgery (debridement and reconstruction) in all cases with good results too[29-32]. Potential benefits of surgery are quicker pain relief, immediate relief of compressed nerve tissue, less kyphosis and fewer relapses. Surgery requires resources and expertise of surgeons, anaesthesiologists and nursing staff. Inexperienced surgeons should not perform these often difficult and technically demanding interventions. Surgery for TB is performed at our institution about five times annually. Complications from operative interventions are not uncommon and include lethal outcome. Surgical procedures vary from drainage or debridement of abscesses to complete resection of the diseased segment, with reconstruction anteriorly and posteriorly with instrumentation techniques.

The main goal of this thesis is to provide insight into spinal TB from a Dutch perspective with special reference to surgery. It is meant to make an inventory of the situation in the Netherlands, to evaluate diagnosis and treatment, and more specifically to analyse the role of the surgeon in spinal TB.

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CHAPTER 2
INCREASE OF BONE AND JOINT TUBERCULOSIS IN THE NETHERLANDS

Increase of Bone and Joint Tuberculosis in The Netherlands
Jutte PC, Loenhout-Rooyackers JH, Borgdorff MW, Van Horn JR
J Bone Joint Surg [Br] 2004;86(6):901-4

ABSTRACT

There has been an increase in the incidence of bone and joint tuberculosis (BJTB) in the Netherlands and we have carried out an epidemiological study in order to find an explanation for this increase. Data from 1993 to 2000 from The Netherlands Tuberculosis Register (NTR) were used. In 1993 there were a total of 52 patients with BJTB. This figure increased gradually to 80 in 1999, before decreasing to 61 in 2000. There was a total of 12447 patients with tuberculosis; BJTB was found in 532 patients, accounting for 4.3% of all cases and 10.6% of all extrapulmonary cases. Localisation in the spine occurred in 56%.

Certain immigrants, in particular patients from Somalia, were more likely to have BJTB than other immigrants or the Dutch population. Increased immigration from endemic countries in recent years explains the observed increase in BJTB incidence. In the Dutch population there was no significant change. Increased age and female gender were associated with BJTB. Only 15% of BJTB patients also suffered from pulmonary tuberculosis. The usual long delay in the diagnosis of BJTB may be shortened if physicians are more alert towards tuberculosis.

INTRODUCTION

There has been an increase in the incidence of bone and joint tuberculosis (BJTB) in the Netherlands during recent years. We have carried out an epidemiological study to find an explanation for this increase and now present a statistical analysis of demographic-, person- and illness-related factors.

PATIENTS AND METHODS

All data were extracted from the Netherlands Tuberculosis Register (NTR) held by the KNCV Tuberculosis Foundation. This register contains data on tuberculosis (TB) patients in the Netherlands from 1993. We have examined the figures from between 1993 and 2000. Every physician in the Netherlands is legally obliged to report a case

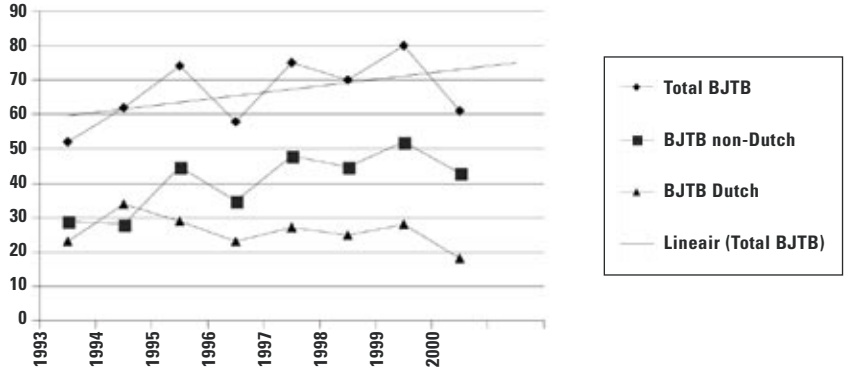
of tuberculosis to the health authorities. In addition, anonymous data are reported by Municipal Health Services to the NTR on a voluntary basis. Data include patient characteristics, diagnosis, bacteriology results (smear, culture), treatment regimens and outcome. All extrapulmonary tuberculosis is classified according to site of the lesion, using the ICD-9 classification. Successful treatment outcome is defined as cure of the patient or completion of treatment[1] . Every immigrant from an endemic area for tuberculosis (incidence greater than 50 per 100.000) has a chest radiograph taken on arrival in the Netherlands. Voluntary screening is carried out every 6 months during the first two years.

RESULTS

The total number of tuberculosis patients was 12447 in the period studied. Pulmonary tuberculosis was present in 7409 patients (60%), and extrapulmonary tuberculosis in 5038 (40%) (Table 1). Of the latter group, 1008 had both pulmonary and extrapulmonary tuberculosis. A total of 532 cases of BJTB was found (Table 1), accounting for 4.3% of all tuberculosis cases and 10.6% of extrapulmonary cases. Of the patients with BJTB, 163 (31%) also had extraskeletal lesions, 50% of which were pulmonary. This means that only 15% of BJTB patients had concurrent pulmonary tuberculosis.

In 1993 a total of 52 patients had BJTB, this figure increased gradually to 80 in 1999, then it decreased to 61 in 2000 (Table 2). Univariate analysis of the incidence of BJTB compared with that of all tuberculosis has shown an increase in BJTB in recent years (Table 2). The decrease in 2000 should be considered a statistical anomaly. The incidence of BJTB for Dutch and non-Dutch people is shown in figure 1; indicating

Figure 1
Total numbers of BJTB from 1993 to 2000.



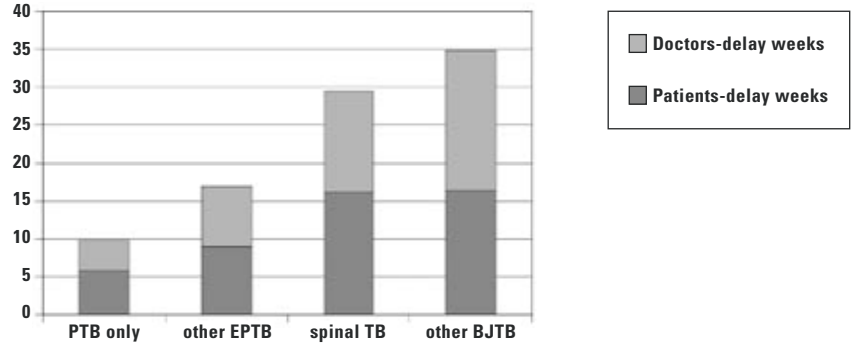
that the increase is restricted to the non-Dutch subjects (r=0.76; 95% confidence interval 0.11-0.95). In the native Dutch population there was no significant change in incidence of BJTB during this period. The Netherlands have a population of 16 million of whom 2.5 million are immigrants. The largest immigrant groups in the year 2000 are from Surinam (280.000), Turkey (270.000), and Morocco (240.000). The incidence of tuberculosis increased from 8.2 in 1987 to 11.8 in 1994, but decreased to 8.9 in 2000. The incidence in 2000 was 3.4 per 100.000 for the Dutch and 136 per 100.000 for immigrants.

Of all patients with tuberculosis, 60% were men and 40% women. In the BJTB group were 261 men and 271 women (49 vs. 51%); (Table 2). Women were relatively more affected by BJTB (OR 1.57). BJTB was associated with increasing age (Table 2) and was more common among Somalians (OR 2.09), and less common among Turks (OR 0.36) and Moroccans (OR 0.68); (Table 2).

The localisation of BJTB was spinal in 308 of the 532 patients (58%) and elsewhere in the skeleton in 224 patients (42%); (Table 1). For spinal tuberculosis compared to all BJTB a decrease was shown with increasing age (Table 3). Spinal tuberculosis was more common among non-Dutch than Dutch patients (Table 1), but this difference is not significant if all nationalities were considered separately (Table 3).

Delay in diagnosis by both patients and doctors is shown in figure 2 for pulmonary, other extrapulmonary, bone and joint, and spinal tuberculosis.

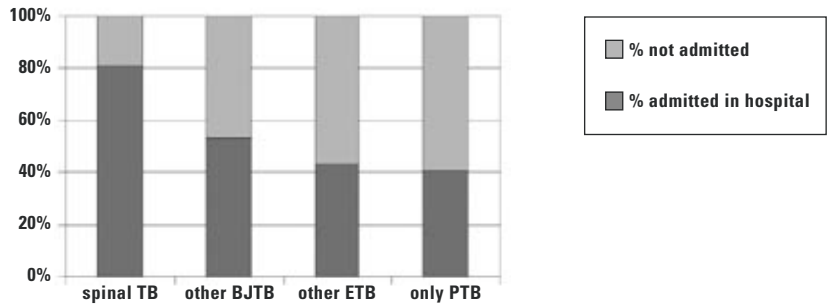
Figure 2
Delay in weeks of patients and doctors for pumonary, extrapulmonary except BJTB, spinal tuberculosis and other BJTB.



The mean delay for spinal tuberculosis was 29 weeks and for other BJTB, 35 weeks. The mean duration of treatment for the various forms of TB is shown in table 4, 340 days for spinal TB and 304 days for other BJTB, compared with 222 days for

pulmonary tuberculosis. The mean duration of hospital admission was 24 days for spinal tuberculosis, 21 days for other BJTB, and 12 days for pulmonary tuberculosis (Table 4). Patients were admitted to hospital in the following proportions: 41% of all pulmonary patients, 43% of other extrapulmonary tuberculosis, 53% of other BJTB, and 80% of spinal tuberculosis (Figure 3). The outcome of treatment was generally good and comparable for all forms (Table 5).

Figure 3
Hospital admission for the various groups of patients with tuberculosis (TB) (ETB=extrapulmonary, PTB=pulmonary).



DISCUSSION

An increase in the incidence of bone and joint tuberculosis was observed between 1993 and 2000. Ethnicity, age and female gender were associated with the disease. Only 15% of BJTB patients also suffered from pulmonary tuberculosis. We noted a significant delay by both patients and doctors between the first symptoms and the commencement of treatment.

There is good evidence that tuberculosis is reported according to the guidelines of notifiable disease, from the close correlation between the actual use of pyrazinamide according to the Dutch Drug Information Project of the Health Care Insurance Board and the data registered with the NTR[2]. Cross-matching of notification data, data from laboratory surveillance, and data in the Netherlands Tuberculosis Register suggest a correlation of 95%. Van Nispen-Dobrescu (unpublished data) evaluated the between-person repeatability of completing the forms. She has shown that repeatability is moderate to good for the variables studied in this report.

Culture results are recorded in the NTR, but the origin of the material from which the cultures were taken was not stated, which means that some assumptions regarding the diagnosis have been made. The only proof for a skeletal lesion is a positive culture of material from the lesion, but even then only 47-81% positive results can be expected[3-5].

There was an increase in the incidence of BJTB from 52 to 80 patients per year between 1993 and 1999. According to statistical analysis, the decrease to 61 in 2000 is considered to be a statistical anomaly rather than a true drop, which we expect to be confirmed by the figures of years to come. Active tuberculosis may be discovered at the obligatory first screening at arrival in the country. Vos et al. have shown that a decade after their arrival, the incidence of tuberculosis among immigrants is still high[6]. Furthermore, a relatively larger percentage develop BJTB. In the native Dutch there was no significant change in incidence during the period studied. The conclusion is that the increase in incidence of BJTB is entirely attributable to immigration.

The fact that certain ethnic groups showed a significantly higher chance of developing BJTB surprised us. This means that, with the same infection prevalence, some ethnic groups progress more often to BJTB and/or less often to other forms of TB. Some previous small series reported that certain ethnic backgrounds were probably associated with higher incidences of skeletal tuberculosis[3,5,7-9]. In a large series from the United States however, ethnicity or country of origin were not associated with BJTB. Increasing age and female gender (adjusted OR 1.7) did show an association similar to our findings[10].

The relatively younger age of the immigrants with BJTB probably reflects the changing general epidemiology of tuberculosis. However, BJTB occurs at a relatively older age if adjusted for nationality. Regarding age, several reports described different age distribution for tuberculosis in whites and non-whites[3,7,10-13]. Possible explanations for this include a different distribution in age groups between various parts of the world, a younger exposure and the varying prevalence with age. From endemic regions it is well known that BJTB commonly involves young children[13]. This is in contrast to our findings. The different chances of progression from infection to disease may also play a role, depending on ethnicity, former habitat and previous contact with the organism concerned.

The spine was the most common site of BJTB, which accords with the literature[7,13]. Spinal tuberculosis was more common among non-Dutch than Dutch patients in our study. Other authors reported similar findings[3,5] .

It must be stressed that only 15% of BJTB patients in our series also suffered from pulmonary tuberculosis. Other authors reported this incidence to be between 20 and 25%[3,8]. A normal chest radiograph does not of course rule out BJTB.

In our study, a lengthy delay by both patients and doctors was found for BJTB (mean period 32 weeks). In France, a mean delay of 12 weeks has been reported[11,14]. The explanation for the long medical delay in the Netherlands is probably a low index

of suspicion and declining expertise[1]. In general, delay in diagnosis increases the risk of a fatal outcome. The long delay for BJTB in this population did not result in greater mortality but less delay must diminish morbidity.

TABLES

Table 1
Details of the site of origin of tuberculosis in Dutch and non-Dutch patients.

	Dutch	Non-Dutch	Total
Spinal TB	105	203	308
other BJTB	102	122	224
other ETB	1604	2902	4506
PTB only	3504	3905	7409
Total	**5315**	**7132**	**12447**

Table 2
Variables in BJTB versus all forms.

Variables	BJTB	Total	Crude OR	Adjusted OR (95% CI)
Year			*p<0.05*	
1993	52	1579	1	
1994	62	1798	1.05	
1995	74	1612	1.41	
1996	58	1657	1.07	
1997	75	1475	1.57	
1998	70	1358	1.60	
1999	80	1545	1.60	
2000	61	1423	1.32	
Sex			*p<0.001*	
Male	261	7429	1	1
Female	271	5018	1.57	1.53 (1.28-1.83)
Age group			*p<0.001*	
<25	93	2989	1	
25-34	149	3372	1.44	1.53 (1.17-1.99)
35-44	72	1973	1.18	1.46 (1.06-2.01)
45-54	63	1150	1.80	2.55(1.81-3.58)
55-64	43	891	1.58	2.42 (1.64-3.57)
65-74	52	909	1.89	2.85 (1.96-4.15)
75+	60	1163	1.69	2.58 (1.77-3.74)
Nationality			*p<0.001*	
Netherlands	207	5315	1	1
Morocco	33	1224	0.68	0.87 (0.59-1.28)
Somalia	123	1572	2.09	3.11 (2.37-4.08)
Turkey	9	621	0.36	0.48 (0.24-0.95)
Other Africa	49	1070	1.18	1.85 (1.31-2.62)
Other Asia	70	1429	1.27	1.61 (1.20-2.17)
Other or missing	41	1216	0.86	1.09 (0.76-1.55)

OR= odds ratio
CI= confidence interval

Table 3
Variables associated with spinal tuberculosis versus all forms of BJTB.

Variables	Spinal TB	All BJTB	Crude OR (95% CI)
Year			*p>0.2*
1993	29	52	1
1994	32	62	0.85
1995	43	74	1.10
1996	33	58	1.05
1997	50	75	1.59
1998	38	70	0.94
1999	50	80	1.32
2000	33	61	0.93
Sex			*p>0.2*
Male	156	261	1
Female	152	271	0.86
Age group			*p<0.05*
<25	49	93	1
25-34	98	149	1.73 (1.02-2.93)
35-44	48	72	1.80 (0.95-3.40)
45-54	39	63	1.46 (0.76-2.80)
55-64	25	43	1.25 (0.60-2.59)
65-74	25	52	0.83 (0.42-1.64)
75+	24	60	0.60 (0.31-1.16)
Nationality			*p>0.05*
Netherlands	105	207	1
Morocco	20	33	1.49
Somalia	71	123	1.33
Turkey	6	9	1.94
Other Africa	34	49	2.20
Other Asia	43	70	1.55
Other or missing	29	41	2.35

OR= odds ratio
CI= confidence interval

Table 4
Mean duration of treatment (days) and hospital admission (days) for the various forms of tuberculosis.

	Duration of treatment	Duration of hospital admission
Spinal TB	340	24
Other ETB	258	12
Other ETB	258	12
PTB only	222	12

Table 5
Treatment outcome from 1993 to 2000. The results are given for 4685 of 5038 (93%) patients with extrapulmonary tuberculosis, and for 6844 of 7409 (92%) patients with pulmonaru tuberculosis, by number and percentage.

	Cured or Treatment completed		Died		Defaulted or transferred out		Total
	Nr	%	Nr	%	Nr	%	
Spinal TB	271	89%	17	6%	18	6%	306
Other BJTB	193	86%	16	7%	15	7%	224
Other ETB	3452	83%	302	7%	401	10%	4155
PTB only	5661	83%	523	8%	660	10%	6844

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CHAPTER 3

MISDIAGNOSIS AND MISTREATMENT OF SPINAL TUBERCULOSIS

Causes of misdiagnosis and mistreatment of spinal tuberculosis with radiotherapy in non-endemic areas - a pitfall in diagnosis and treatment: hazards of radiotherapy on the tuberculous lesion

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ABSTRACT

This is a report of a previously undescribed misdiagnosis and subsequent mistreatment with radiation for tuberculosis of the spine. Two patients received radiotherapy on spinal lesions of suspected malignant origin. In both patients the lesions were of tuberculous origin and the lesions increased during radiotherapy. In case 2 the paraplegia did not heal.

It is not seldom that radiation therapy is provided for suspected malignant spinal lesions without histological confirmation. Literature is not available on harmful effects of radiation therapy for tuberculosis of the spine. Radiotherapy locally aggravates tuberculous spinal lesions. In case of a spinal lesion of unknown origin, tuberculosis should always be considered. Adequate biopsy for cultures and histology is mandatory. Open surgical biopsy can provide sufficient material and instant decompression.

INTRODUCTION

Radiation therapy holds a fundamental role in oncological emergencies. In responding patients, it is associated with an improved quality of life and a longer survival time[1]. It is not seldom that radiation therapy is provided for suspected malignant spinal lesions without histological confirmation. In our institution this happens approximately 5 times annually. No data on this were found in the literature.

The distinction in imaging studies between tuberculosis (TB) and malignancies of the spine can be difficult. Throughout the years, several reports have addressed this topic[2-6]. Data on the frequency of this diagnostic dilemma could not be found. Until three decades ago, reports on non-endemic tuberculous areas addressed the importance of tumours in differential diagnostics of spinal tuberculosis[7]. This was gradually reversed to stressing the importance of TB in differential diagnostics of tumour metastasis as the incidence and importance of TB in many countries diminished[8,9].

In non-endemic areas for TB, spinal tuberculosis or Pott's disease is a forgotten diagnosis. We report 2 cases with a previously undescribed misdiagnosis and subsequent mistreatment with radiotherapy for tuberculosis of the spine. In doing so, we hope to promote awareness for tuberculosis in non-endemic areas.

ILLUSTRATIVE CASES

Case 1

A 26-year-old man, a refugee living in the Netherlands for 3 years, came to our institution with a 3-month history of backache. He was HIV-negative and had been medically treated for 2 years for chronic myeloid leukaemia (CML). Normal radiographs revealed no abnormalities in the painful thoracic area; 2 fused vertebrae were seen in the lumbar spine: L1-2. Chest X-ray was normal. Laboratory work-up showed elevated leucocytes 12.6 10^9/L (4.0-10.0) and low haemoglobin 7.3 mmol/L (8.7-11.2), C-reactive protein (CRP) was only slightly elevated at 21 (0-10), and raised erythrocyte sedimentation rate (ESR) was 80 mm (<10). Mantoux test was not performed.

Magnetic Resonance Imaging (MRI) without contrast enhancement showed a paravertebral mass left of Th8 (Figure 1a). Radiological differential diagnosis included

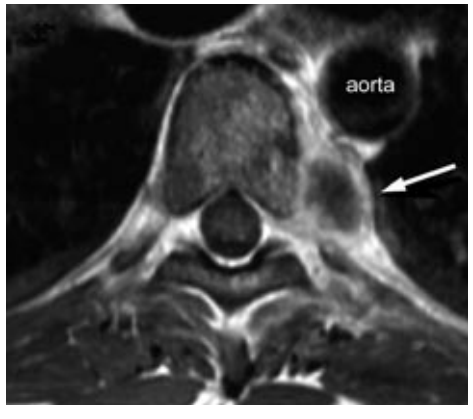


Figure 1a
Transverse MRI showing a paravertebral mass (arrow) on the medial side of the descending aorta at the level Th8-9.

chloroma, metastasis, and abscess of bacterial or tuberculous origin. A Computer Tomography (CT) guided fine-needle aspiration was performed since the lesion had a close relationship with the pleura and the intervertebral foramen. The risk of creating a pneumothorax with a trochar biopsy was considered too high. Only cytologic examination could be performed and no histology. The specimen of 20 ml. was poor in cells, and showed only erythrocytes and some atypical myeloid cells with enlarged

polymorphic nuclei, some lymphoid cells, fibroblasts and muscle cells. Tuberculosis was considered but could not be confirmed by Polymerase Chain Reaction (PCR) and acid-fast bacilli stain, as both were negative. Cultures for TB were not performed.

Diagnosis chloroma was suspected, based on the known association with CML, and radiation therapy started. A total dose of 16 Gray was given. A second MRI, two months after the first, showed an increase of the paravertebral mass from Th8 to Th10 and a new partial destruction of the arches of Th8 and Th9 (Figure 1b).

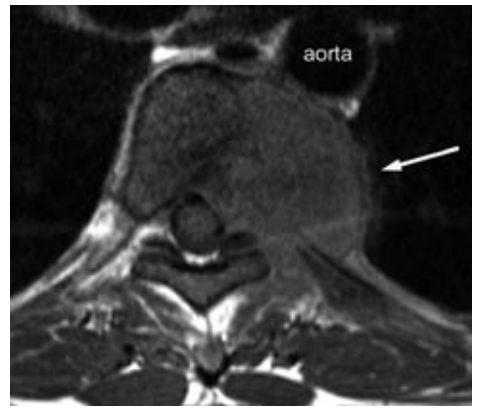


Figure 1b
Transverse MRI at the same level made 2 months later clearly demonstrates increase of the paravertebral mass (arrow) with partial destruction of the arches of Th9. The aorta is pushed anteriorly.

The backache had worsened. After the second MRI a surgical biopsy was performed of the paravertebral mass. Histologic examination showed caseous granulomatous necrotic tissue, suspect for tuberculosis. Tuberculosis therapy was started according to protocol: 2 months of pyrazinamid and ethambutol and 6 months of isoniazid and rifampin. The PCR and acid-fast bacilli stain of the specimen again were negative, but the culture became positive after four weeks with a fully sensitive *Mycobacterium tuberculosis*. Treatment result regarding tuberculosis was good, the painful lesion subsided and there was no relapse.

Case 2

A 55-year-old man came to another hospital with signs of paraplegia. He had loss of motor function of the legs, and loss of sphincter control of bladder and rectum. He had been well up until 1 month earlier, when he started suffering from low backache and mild paresthesia of both legs. On admission he had an incomplete motor and sensory paraplegia (Frankel grade C), at level Th11. Routine biochemical and haematological investigations were normal, CRP was 14, and ESR was mildly elevated at 40 mm. His chest X-ray showed calcified hilar lymph nodes. Previous radiographs revealed a fusion of C4-5 of the cervical spine and there were signs of post-infectious

calcified arthritis in both hips, the left knee joint and both ankles. Overview of the abdomen showed multiple mesenteric calcifications. Radiographs of the thoracic spine at first presentation showed (in retrospection) a paravertebral mass at the lower thoracic vertebrae (Figure 2). MRI revealed a destructive lesion with abscess

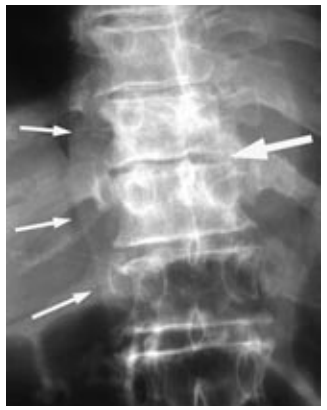


Figure 2
Radiograph showing widening of the paravertebral soft tissue shadow in the lower thoracic area (small arrow), and a slight decrease of the intervertebral distance Th9-10 (large arrow).

formation and spinal cord compression at Th11-Th12 with disc destruction (Figures 3a and 3b). CT-guided trochar biopsy of the lesion did not reveal a diagnosis due to an insufficient amount of mainly necrotic tissue. There were no further attempts

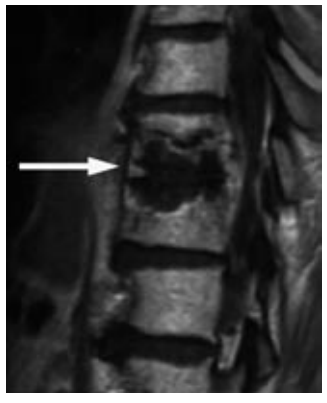


Figure 3a
T1-weighted MRI with a destructive lesion in Th11 and Th12, with disc destruction (arrow).

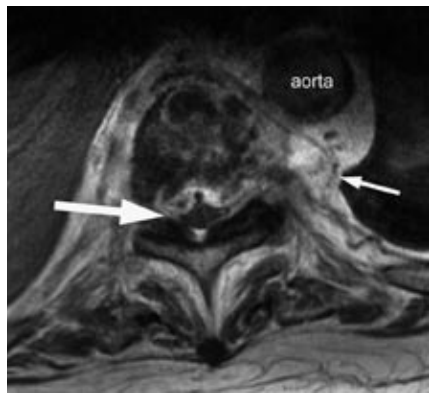
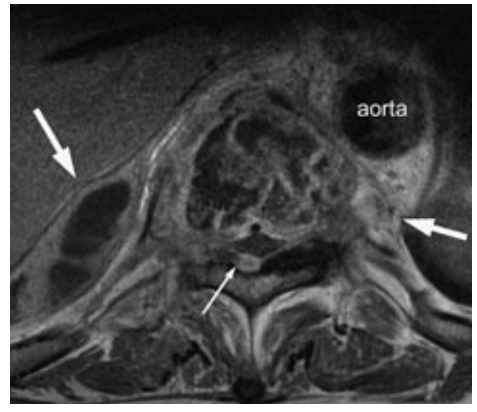


Figure 3b
Transverse T1-weighted MRI showing a mass in the vertebral body, narrowing the spinal canal (large arrow) and extending on the left (small arrow).

to obtain material from the lesion. The primary care physician made a diagnosis of metastasis. Tuberculosis was never considered in differential diagnostics. The neurological deficit had already been present for some weeks. The treating physicians did not expect an improvement of neurological function by surgical means, and the aim of treatment was to prevent further deterioration with radiotherapy. During the course of radiation, because of clinical worsening and progression of the paresis, corticosteroids in high doses were added. Laboratory parameters had also worsened: ESR was raised to 120 mm, Hb had decreased to 5.7, and he had developed leucopenia at 1.5.

Six weeks later he was critically ill; a sputum sample revealed acid-fast bacilli. The next day, with the diagnosis of disseminated tuberculosis, he was transferred to our tuberculosis unit. Tuberculosis treatment was started: 2 months of pyrazinamid and ethambutol and 6 months of isoniazid and rifampin. MRI scan at that time revealed progression of the lesion and abscess formation on both sides of the spine (figure 3c). The tuberculosis was cured, but regrettably there was no reversal of the neurological deficit.

Figure 3c
Transverse T2-weighted MRI made 6 weeks later with increase of the mass in the vertebral body, a still-narrow spinal canal (small arrow) and expansion in the soft tissue to both left and right (large arrows).



DISCUSSION

Two patients are reported with a previously undescribed misdiagnosis and subsequent mistreatment with radiotherapy for tuberculosis of the spine. During radiotherapy both lesions increased, in case 2 the paraplegia did not heal. One of the reasons for misdiagnosis was probably the low incidence of tuberculosis in the Netherlands, as it is one of the countries approaching the elimination phase of tuberculosis, and so spinal tuberculosis is a forgotten diagnosis[10]. At present, approximately 40

new patients are seen nationwide in the Netherlands (population 16,000,000)[11]. With decreasing incidence, clinical expertise declines too[10]. This results in a lack of experience in recognising tuberculosis in imaging studies and a low index of suspicion. Average delay in the Netherlands for the year 2000 in diagnosis for spinal TB was 29 weeks[11].

The work-up of patients with spinal lesions of unknown origin should include the search for TB. It starts with a thorough history-taking. Anamnesis and past medical history can be very helpful in diagnosing TB. The risk of developing tuberculosis increases manifold if a patient belongs to a risk factor group that includes inmates and staff of correctional facilities, residents and staff of nursing homes, homeless people, health care workers, prostitutes, substance abusers, immigrants from endemic areas, immunocompromised people, and people with a past history of TB[12]. In the patients presented here, solely from an anamnestic point of view, TB should have been suspected and adequate actions taken. Patient 1 was an immigrant from an endemic area who used immunosuppressive medication. History in case 2 revealed coxitis tuberculosa at the age of 7. This was just before the start of the tuberculostatic era, and he was never treated subsequently with tuberculostatic drugs.

Immunosuppression is a well-known risk factor for TB. In a series of bone marrow transplant recipients, 5.5% developed tuberculosis, mainly via disruption of host reconstitution of immune defenses[13]. Therefore we agree with Karnak et al. that it seems highly likely that radiation therapy will locally aggravate the destructive tuberculous process by diminishing local immune responses[14]. In both patients the radiotherapy was finished before the chemotherapy started. The local response to the tuberculosis drugs was good in both cases and did not show diminished healing.

Work-up often comprises a Mantoux test. In neither of the two cases presented here was a Mantoux test performed. It is questionable whether the test would have aided in diagnosis. Since patient 1 was an immigrant from an endemic country, and patient 2 was born in a period when TB was very common, both would probably have had a positive test; this would however not prove active disease. A negative test in case 1 would not have been helpful either, because of the possibility of a false-negative tuberculin reaction in immunosuppressive patients[12].

Chest X-ray will only be positive in 15% of people with bone and joint tuberculosis[11]. Normal radiographs may not be sufficient for diagnosis of spinal TB, especially in non-endemic countries. However, in both patients presented here, radiographs showed fused vertebrae at other levels, most likely to be signs of previous spinal TB. In case 2 radiographs showed a paravertebral mass at the lower thoracic vertebrae, a sign of the infectious nature of the lesion (Figure 3). The characteristic radiological image of an active tuberculous spondylitis is that of affected vertebral bodies on both sides of a destroyed disc. Vertebral collapse and abscess formation are

important radiological clues as well[3-5]. CT and MRI can accurately assess formation and extent of abscesses, as well as narrowing of the spinal canal. A septic spondylitis usually gives instant symptoms, while a tuberculous lesion has a much more insidious onset. Because of the relatively slow onset of TB, large abscesses can develop with huge bony destruction before clinical symptoms are prevalent[15]. MRI scans showed in both cases the typical signs of an abscess, hardly compatible with malignancy. Tumour expansion can give a paravertebral mass like the one shown in Figure 3, but without abscess formation[5,15]. In both cases presented here, the infectious nature of the disease should have been identified based on imaging studies. In case 1, based on MRI findings infection was considered, even tuberculosis, however this diagnosis was discarded because of the negative results of the PCR and acid stain.

Preferably material from the lesion should be acquired for PCR, acid stain, cultures and histology. In both cases, cultures for TB should have been performed. The only definite proof for a skeletal lesion is a positive culture of material from the lesion, but even then only 47-81% positive results can be expected[16-19]. A CT-guided biopsy is a minimally invasive way to provide tissue from a lesion for further analysis. It is essential to harvest sufficient material for histology and cultures. It is mandatory to specifically ask the pathologist to consider tuberculosis. In both cases presented here, diagnosis was not established on biopsy material, probably due to insufficient amounts. Surgical biopsy should have been performed. In case 1 the fine needle aspiration revealed fluid; this should have been suspected as a product of infection in the absence of central massive tumour necrosis. In case 2, the treating physicians were convinced of the metastasis diagnosis, in spite of the previous history of tuberculosis and the abscess formation on MRI (2 clues for the diagnosis of TB). If metastasis had been the correct diagnosis, radiation therapy could have been indicated.[1] Since the paraplegia had already been present for some weeks, the treating physicians did not expect a recovery with either surgery or radiotherapy. Aim of radiation was prevention of further deterioration. Surgery should have been performed. There is of course no certainty as to what the effect on the neurological status would have been. In this patient the local lesion progressed, so there was virtually no chance of neurological recovery; surgery however would have provided instant decompression as well as sufficient biopsy material.

Laboratory parameters in general are not very helpful in tuberculosis. ESR can be elevated and so can CRP. In both cases ESR values were elevated, compatible with both malignancy and infection. CRP values were hardly elevated in both patients, making the possibility of an infectious cause for the lesions less likely. A high CRP would certainly have raised the suspicion of an infection. Tuberculous infection may very well be accompanied by a low CRP.

In neither case presented here was there an histological confirmation of the diagnosis. In our institute, about 5 patients receive radiotherapy without histologic

proof of metastasis each year. These are patients with an acute onset of neurological symptoms. In our hospital we try to start therapy within 24 hours of onset of symptoms. This can be either radiotherapy or surgical decompression followed by radiotherapy. Recent evidence suggests that surgical decompression, stabilisation and subsequent radiation therapy is superior to radiation therapy alone: patients treated with additional surgery retained the ability to walk longer and regained the ability to walk more often than patients without surgical decompression[20]. In all patients with suspected metastasis of unknown origin, screening is done for the most obvious primary lesions: prostate specific antigen, radiographs of breast and chest. If this reveals a primary lesion, radiation therapy is started. If not, histology is mandatory. Radiation therapy should only be applied in the presence of a clear histologic diagnosis, ruling out tuberculosis. Radiation is an aggressive and potentially harmful therapy, like surgery. It is not good practice to start a potentially harmful treatment in case of failed biopsy. Especially for patients without neurological deficit, secondary trochar biopsy, or even open biopsy, is indicated. In patients following spinal radiation treatment, spondylodiscitis is not a very uncommon diagnosis[21], and such therapy can be locally destructive for this condition. This also applies to tuberculous spondylitis. In case 2, no neurological recovery was substantiated, while in most cases active tuberculosis with paraplegia can be treated successfully by conservative or surgical means[16, 22].

Furthermore, if the suspicion of tuberculosis is high or the patient is seriously ill with a disorder that is thought to possibly be tuberculosis, tuberculostatic therapy should be initiated promptly – often even before smear results are known and usually before mycobacterial culture results have been obtained. If the diagnosis is confirmed by isolation of *M. tuberculosis* or a positive PCR test, treatment can be continued. When the initial acid-fast bacilli smears and cultures are negative, a diagnosis other than tuberculosis should be considered and appropriate evaluations undertaken. If there is a clinical or radiographic response within 2 months of initiation of therapy and no other diagnosis has been established, a diagnosis of culture-negative tuberculosis can be made and treatment continued[23].

In difficult cases, a double diagnosis should be considered too. TB has been reported to complicate malignancy[14,24]. Deterioration of immunity due to the tumour itself, chemotherapeutics or radiotherapy may play a role in the reactivation of tuberculosis. Pulmonary infections encountered in carcinoma patients or aged people should raise the suspicion of tuberculosis reactivation, especially in endemic countries[14, 24]. A patient with spinal cord compression due to multiple myeloma and spinal tuberculosis was recently reported[25].

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CHAPTER 4

CHEMOTHERAPEUTIC TREATMENT FOR SPINAL TUBERCULOSIS

Chemotherapeutic treatment for spinal tuberculosis

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Int J Tuberc Lung Dis 2002;6(3):259-65

ABSTRACT

This literature review was done to evaluate whether 6 months of chemotherapy for patients with spinal tuberculosis prevents relapse as effectively as more than 6 months of chemotherapy.

Medline search was performed including references, from January 1978 to November 2000. Inclusion criteria for publications: diagnosis of spinal tuberculosis confirmed bacteriologically and/or histologically, or probable on the basis of clinical and radiological parameters; treatment regimen (whether or not in combination with surgery) included isoniazid (ISO), rifampicin (RIF) and pyrazinamide (PYR); follow-up period after completion of treatment of 12 months or more. Exclusion criteria: patients with relapse who had previously been treated adequately for tuberculosis. Outcome parameters: Relapse rate.

Four publications were found with ISO/RIF/PYR regimens of 6 months duration and 10 publications with ISO/RIF/PYR regimens of > 6 months duration. A number of patients had received ISO/RIF and ethambutol (ETH) for ≥ 9 months. In the results, no distinction was made between treatment groups. ISO/RIF/PYR for 6 months led to a relapse rate of 0% (0/56) (95%CI 0.0-6.4); follow-up after surgical intervention ranged from 6 to 108 months. ISO/RIF/PYR for ≥ 9 months (≥119 patients) or ISO/RIF/ETH for ≥ 9 months (≤ 71 patients) led to a relapse rate of 2% (4/218) (95% CI 0.6-5.0); follow-up after surgical intervention was 6-168 months.

It was concluded that despite the small number of studies 6 months of therapy is probably sufficient for patients with spinal tuberculosis.

INTRODUCTION

In the literature, there is no uniformity in the duration of chemotherapeutic treatment for spinal tuberculosis. The American Thoracic Society (ATS) recommends 6 months treatment for spinal tuberculosis and osteoarticular tuberculosis in adults, but 12 months in children, because reliable data on shorter treatment durations are lacking[1]. The British Thoracic Society (BTS) recommends 6 months treatment,

irrespective of the age of the patient[2]. The Netherlands Tuberculosis Register (NTR) shows that in the period 1993-1998, 384 patients were treated for osteoarticular tuberculosis (55% had spinal tuberculosis); 22% (86/384) were treated for 6-9 months, 31% (119/384) were treated for 10-12 months and 32% (123/384) were treated for ≥ 13 months. The treatment regimens included isoniazid (ISO), rifampicin (RIF) and pyrazinamide (PYR).

In patients with spinal tuberculosis, surgical intervention is very important. It may comprise abscess drainage, debridement, laminectomy, anterior and/or posterior stabilisation with bone grafts or metal implants.

The aim of this study was to investigate whether 6 months of chemotherapeutic treatment with a regimen including ISO, RIF and PYR (6IRP), with or without surgery, was equally as effective as a longer treatment regimen (> 6 months). Outcome was evaluated in terms of relapse rates after successful treatment.

METHODS

A search was made of the English, German and French literature published subsequent to 1978 (i.e., after the introduction of pyrazinamide) using Medline; the references were checked for additional relevant publications. The most recent search was performed in November 2000. Keywords were: osteoarticular, miliary, spinal tuberculosis, drug therapy; searches were also made under Pott's disease, vertebral tuberculosis, bone, joint tuberculosis, treatment, antitubercular agents, isoniazid, rifampicin and pyrazinamide.

Inclusion criteria were: study populations of patients with spinal tuberculosis whose treatment had included ISO, RIF and PYR, and in whom the follow-up period after the completion of treatment was at least 12 months.

The criterion for exclusion was patients with tuberculosis relapse who had previously received adequate treatment with chemotherapy. The chance of resistance being induced by inadequacies in therapies in the past is considered higher in this group, thereby rendering the prognosis for the group more unfavourable.

DEFINITIONS

Diagnosis

The diagnosis of spinal tuberculosis is certain when Löwenstein culture of biopsy specimens obtained from the vertebrae are positive; the diagnosis is almost certain in the case of a histological profile with caseating granulomas; the diagnosis is probable when there is no bacteriological and/or histological evidence of tuberculosis in the vertebral column, but active tuberculosis has been proven biologically in other body compartments (e.g., positive urine culture, positive sputum or positive stomach contents after fasting) in combination with clinical or radiological manifestations (X-ray, computed tomography [CT] scan, magnetic resonance imaging [MRI]) that correlate with spinal tuberculosis and a good reaction to chemotherapy.

Clinical symptoms vary widely, but usually comprise pain with an acute or gradual onset, whether or not in combination with neurological deficits, fever and elevated erythrocyte sedimentation rate (ESR). It is common for several vertebrae to be affected, including the vertebral discs. Paraspinal and/or epidural abscesses may be present.

The diagnosis should be considered in patients who belong to the risk groups for tuberculosis and have corresponding clinical and radiological symptoms with a good reaction to chemotherapy.

Successful treatment

Treatment is considered to be successful when the symptoms have subsided or the patient is complaint-free, the neurological deficits have improved or disappeared, there are no longer any clinical signs of abscesses or sinuses, the vertebral column is stable and the patient is able to resume full activities.

Radiological characteristics of successful treatment are: radiologically quiescent lesion, bony fusion with little or no deformity. During (sufficiently long) follow-up, there must be no signs of progression of the kyphosis and no relapse of the tuberculosis [3,4]. It should be realised that the risk of kyphosis and paraplegia also depends on the surgical intervention at an earlier stage [3,5,6]. There is a risk of kyphotic deterioration until bony fusion has occurred, even when the clinical profile is stable [3]. In children in the growth phase, the risk of kyphotic deterioration is greater than in adults.

Failure

Failure means that the complaints deteriorate during treatment and changes have to be made to the chemotherapy regimen. Failure does not necessarily have to be proven bacteriologically and/or histologically.

Relapse

Relapse refers to the situation in which the complaints recur after the completion of successful treatment, where, on the basis of the complaints, radiodiagnostics, CT scan and MRI, whether or not in combination with biopsy, it is necessary to start a new course of chemotherapy.

Publications with a 6-month treatment regimen

There were 4 publications with a 6-month treatment regimen of isoniazid, rifampicin and pyrazinamide (6IRP) (Tables 1 and 2) [7-10]. In each publication, a number of patients also received 18 months treatment with isoniazid, rifampicin and ethambutol (18IRE). In the discussion of the results, no distinction was made between the patients who had followed different treatment regimens. In the publications, there was a total of 82 adult patients (68% men, 32% women). There was no mention of whether human immunodeficiency virus (HIV) testing had been performed. Chemotherapy was dosed according to the World Health Organisation (WHO) guidelines [7-9,21]. Nothing was mentioned about administering the chemotherapy under supervision. All the patients had undergone surgical intervention, usually within 3-4 weeks of starting chemotherapy. The interval between the onset of complaints and intervention varied from 1-12 months in 67% of the patients [9,10] and from 6-12 months in 33% [7,8].

The localisation of the affected vertebrae was as follows: cervical 23%; thoracic 21%; thoracolumbar 17%; lumbar 40% and lumbosacral 1/82; there were double localisations in 3 patients [9]. In 48% of the patients, one vertebra was affected; in 34% of the patients, two vertebrae were affected and in 18% of the patients, three vertebrae were affected.

Neurological deficits were present in 60% of the patients; 18% were known to have an abscess preoperatively and 6 had a fistula [10]. The diagnosis had not been proven bacteriologically in any of the patients, but the histological profile corresponded with tuberculosis in 55%.

After the completion of treatment, all the patients were declared cured. The neurological deficits had improved in 48/49 patients, but 8 patients had not recovered completely. In 3/6 patients the fistula persisted; surgical intervention was necessary in two of them [10]. The interval until radiological consolidation was 3-5 months in all the patients. All 82 patients completed postoperative follow-up (duration: 6-108 months). The relapse rate was 0%.

Publications with a > 6-month treatment regimen

There were 10 publications with a > 6-month treatment regimen of isoniazid, rifampicin and pyrazinamide (≥ 9 IRP) (Tables 1 and 2) [11-20]. Three publications also reported on patients who had not received PYR [14,19,20]. When presenting the results, no distinction had been made between the patients who had received PYR and those who had not.

The results of these 10 studies were as follows: in a total of 344 patients (56% men, 44% women), 274 had spinal tuberculosis. Only one publication mentioned HIV testing: none of the seven patients tested were found to be HIV-positive [16]. Age distribution was as follows: 79% (216/274) were adults [11,14,15,18-20]; 2% (6/274) were < 12 years [13]; 19% (52/274) comprised adults and children [12,16,17]. In 4/10 publications, chemotherapy was dosed according to the WHO guidelines [11,15,16,18,21]. The actual treatment regimen was not mentioned in 2/10 [12,16]. Nothing was mentioned about administering the chemotherapy under supervision. Surgery was performed in 59.7% (162/274) and 40.9% (112/274) did not undergo surgery. The interval between the onset of symptoms and chemotherapy and/or surgery varied from 2 weeks to 39 months; in 60% (165/274), the average duration was 6 months [11,12,14,18,20]. The time of surgery in relation with the start of chemotherapy was not always mentioned [11-14,16,17,19].

The localisation of the affected vertebrae was as follows: cervical 4% (7/199); cervicothoracic 1 patient (1/199); thoracic 51% (102/199); thoracolumbar 14% (27/199); lumbar 29% (57/199); lumbosacral in 0.5% (1/199); double localisations were present (thoracic and cervical) in four patients. In one publication on 75 patients with spondylitis, the precise localisations were not mentioned [20]. The number of affected vertebrae was not mentioned in 64 patients [12,14,16]. One vertebra was affected in 24% of the 210 patients, while more than one was affected in 76%. Neurological deficits were reported in 53% (144/274); paravertebral abscesses were present in 102 patients and epidural abscesses in 41 [11-13,15,16,19,20].

On the basis of the vertebral biopsy specimens, the diagnosis was confirmed bacteriologically in 62% (114/183), histologically in 72% (87/121) [17,19,20] and bacteriologically and/or histologically in 50/58 patients [11,15]. The diagnosis was confirmed bacteriologically and histologically from a biopsy specimen obtained from a different location in 26 and three patients, respectively [12,14,18,19]. Isoniazid resistance was present in 5/70 patients [11,20]. Failures occurred in 10/42 patients, whether or not they received PYR and whether or not they received surgery [19]. Nussbaum et al. stated that a treatment duration of < 6 months led to relapse[12]. Their patients received varying combinations of ISO/RIF/PYR/ETH and streptomycin (STR) for at least 3 months. Progression of the symptoms was observed in a total of 13/29 patients 2 months to 14 years after diagnosis; no distinction was made between failures and relapse and it was not mentioned whether a new course of chemotherapy had been started. One patient died within 1 month of starting treatment. The average follow-up period in the 28 remaining patients was 7.4 years (1-20 years); one patient died, 17 patients had mild or no residual neurological deficits and 10 patients had severe residual neurological deficits [12].

When the 29 patients who had received ≥ 3 ISO/RIF/PYR/ETH/STR in the study by Nussbaum were omitted from the analyses, the results were as follows: 3% of the patients died before completing treatment (8/245); seven out of these eight patients died of other causes [11,15,19,20]. A total of 93% were cured (227/245). After the completion of treatment, 9% had residual neurological deficits [11,13,17,19]. Bony fusion

had occurred in all the cases (16/16) [13,18], in 36/57 within 3 months and in 56/57 within 6 months [15,17].

Follow-up duration after surgical intervention varied from 6-168 months. Relapse occurred in 2% (4/218). It is unclear whether they had received pyrazinamide and/or surgery [19,20]. Colmenero et al. reported relapse in three patients (3/29=10%); follow-up duration was 6 months after the completion of treatment [19]. Pertuiset reported relapse in 1 patient (1/73=1%); follow-up duration was 12.3 months ± 21 months. The patient was treated for 9 months [20].

DISCUSSION

Very few reports have been published on the results of 6 months treatment with isoniazid, rifampicin and pyrazinamide in spinal tuberculosis patients [7-10]. This might be because surgical intervention forms an essential part of treatment and the literature has focused more attention on this aspect [3-6,11,12]. It is unclear whether there is overlap in the patients described by Loembe et al. [8,9]. In most cases, the follow-up duration after surgical intervention is mentioned, not the duration after the completion of chemotherapy. It was not possible to establish how many patients had completed a follow-up of ≥ 12 months after chemotherapy. All the patients who received 6 months chemotherapy had also received surgery. Relapse only occurred in the group that had been treated for longer than 6 months. It was unclear whether the patients with relapse had received pyrazinamide, whether they had undergone surgery or had an indication for surgery. On the other hand, the relapse rate of 2% (4/218, 95%CI 0.6-5.0) is so low that this does not justify treatment for a period of more than 6 months, especially in the view of the good results in the group of patients treated 6 months. The relapse rate for this group was 0% (0/56, 95%CI 0.0-6.4). Insofar as data are available, the penetration of chemotherapy in spinal tuberculosis lesions is good [22]. Surgery accelerates the resolution of sinuses and abscesses and reduces the risk of their development [23]. In the case of progression or persistence of abscesses and/or neurological deficits during chemotherapy, surgical intervention should be considered [11,24]. Not only the risk of relapse, but also the risk of kyphotic deterioration and late neurological complications justify a long follow-up period [3,6].

Another explanation for the small number of studies might be that even after treatment with 6 HR and a follow-up of ≥ 3 years, the relapse rate was low [25,26]. It may be possible to administer fewer chemotherapeutics to patients with spinal tuberculosis, because the bacterial load is much lower than that in lung tuberculosis [25,27]. The risk of primary resistance developing through spontaneous mutation is lower in the case of low bacterial concentration. However, tuberculosis can be active in several organs simultaneously, which necessitates an intensive phase with three chemotherapeutics (ISO/RIF/PYR) for *M. tuberculosis* with normal sensitivity.

Moreover, in contrast with the period in which the British Medical Research Council (MRC) studies were performed [25,28], there is a greater risk nowadays of becoming infected with a primary resistant strain. An intensive phase with four chemotherapeutics (ISO/RIF/PYR/ETH) is necessary if the resistance pattern is unknown.

The question arises as to why patients are treated for longer than 6 months. A possible explanation is that there is doubt about the parameters for declaring a patient "cured". There might be doubt about the radiological quiescence of the affected vertebra. The clinical profile can be stable even when bony fusion is incomplete [3].

The MRC studies have shown that further improvement of the radiological profile occurs even after the chemotherapy has stopped, but the kyphosis can still deteriorate [25,28]. The risk of kyphotic deterioration is greatest (i) in children under 15 years, in whom ≥ 3 thoracic vertebrae are affected, (ii) in patients in whom the disease spreads from 1-2 vertebrae to 3-4 vertebrae, and (iii) in patients with an initial angle of > 30° [6]. Chemotherapy in patients with spinal tuberculosis is obligatory, but careful monitoring is necessary in order to perform surgery as soon as there is an indication [3,6,11,23]. Surgery may comprise abscess drainage, debridement, laminectomy, anterior and/or posterior stabilisation with bone grafts or metal implants. The following circumstances are generally considered as indications for surgical intervention: 1) neurological deficits (with acute or non-acute onset) caused by compression of the spinal cord; 2) spinal instability caused by collapse or destruction of vertebrae, or kyphosis of more than 30°; 3) no response to chemotherapeutic treatment; 4) non-diagnostic biopsy; 5) large paraspinal abscesses [11,12,29].

It is very unlikely that this literature analysis included patients known to be HIV-positive. The clinical profile and chemotherapeutic regimen would be the same as that in HIV-negative patients [30].

Conclusions and recommendations

On the basis of this literature analysis, it can be concluded that the treatment for spinal tuberculosis does not differ from that for lung tuberculosis. The treatment regimen comprised two months ISO/RIF/PYR followed by four months ISO/RIF for *M. tuberculosis* with normal sensitivity. If there are indications of resistance, four chemotherapeutics (ISO/RIF/PYR/ETH) should be administered while awaiting the result of the resistance pattern. If the resistance pattern remains unknown, then ethambutol should be continued throughout treatment. The necessity for surgical intervention should be considered separately for each individual [3,29]. A separate study on the effectiveness of surgical intervention in combination with chemotherapeutics is planned.

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TABLES

Table 1

Publications with study populations of patients with spinal tuberculosis, treated with or without surgery for 6 months or >9 months with isoniazid (I), rifampicin (R) and pyrazinamide (P), with or without ethambutol (E) and/or streptomycin (S). The cure rate in the patients who started treatment and the relapse rate are shown. The postoperative follow-up period is given in months. The number preceding the treatment regimen is the treatment duration in months (see next page).

Author	Regimen	sur-gery	No. of patients	Cure rate	Follow-up in months mean (range)	Relapses
Loembe[7]	6IRPE	+	3	100%	32 (8–96)	0/3
	18 IRE	+	2	100%		0/2
Loembe & Chouteau[8]	6IRPE	+	14	100%	23.7 (8–96)	0/14
	18IRE	+	8	100%		0/8
Loembe[9]	6IIRPE	+	18	100%	6–108	0/18
	18IRE	+	8	100%		0/8
Ghadouane et al.[10]	6IRPS	+	21	100%	15.6 (8–60)	0/21
	12–18IRE	+	8	100%		0/8
Rezai et al.[11]	>18IRPE	-	9	100%	12 (12–60)	0/18
	12IRPE	+	9	78%		
	RPE (I-resistant)	+	2	2 deaths TB-		
Nussbaum et al.[12]	>3 months IRPES combinations	+25 -4	29	1 death <1 month treatment	7.4 years (1–20)	13 patients readmitted 2 months–14 years after the initial diagnosis
Journeau et al.[13]	3IRPE/2IRE/7IR	+	6	100%	12–168	0/6
Perronne et al.[14]	3IRPE/IR	+1 -22	23	100%	>12	0/22 (9/31 lost)
	3IRE/IR (9–18IR, median 12IR)	-8	8	100%		
Yilmaz et al.[15]	2IRPS/7IR	+	38	97% 1 death TB-	29 (24–76)	0/37
Vohra et al.[16]	>9IRPE	+19 -6	4/25 spinal TB	100%	41 (13–96)	0/4 (0/25)
Louw[17]	12IRPE	+	19	100%	25.5 (6–47)	0/19
Güven et al.[18]	IRP, mean 11 months	+	10	100%	24.2 (17–36)	0/10
Colmenero et al.[19]	2IR(P)(E)/7–10HR	+32 -10	42	69% 10 failures, 3 deaths TB-	6 months after completion of treatment	3/29
Pertuiset et al.[20]	3IRPE/...	+20 -55	52	97% 2 deaths, 1 TB+ and 1 TB-	12.3 ± 21	1/73
	3IRE/... mean 14.7 ± 3.4 months		21			

Table 2

Spinal tuberculosis patient characteristics and treatment regimens with isoniazid (I), rifampicin (R) and pyrazinamide (P), whether or not in combination with ethambutol (E) and/or streptomycin (S) [7–20] (see next page).

	6IRP	≥ 9IRP
No. of patients	56/82	274/344
Age		
Adults	82	79% (216/274)
Children < 12 years		2% (6/274)
Adults and children		19% (52/274)
Sex male:female	68%:32% (56:26, n = 82)	56%:44% (192:152, n = 344)
Delay		
1–12 months	67% (55/82)	
6–12 months	33% (27/82)	
mean 6 months		60% (165/274)
Localisation of affected vertebra		
Cervical	23% (19/82)	4% (7/199)
Cervico-thoracic		1 patient
Thoracic	21% (17/82)	51% (102/199)
Thoracic lumbar	17% (14/82)	14% (27/199)
Lumbar	40% (32/82)	29% (57/199)
Lumbosacral	1 patient	1 patient
		4 patients cervical and thoracic
Unknown		75
No. of affected vertebrae		
1 vertebra	48% (39/820)	24% (51/210)
> 1		76% (159/210)
2	34% (28/82)	
3	18% (15/82)	
Unknown		64 patients (n = 274)
Neurological deficits	60% (49/82)	53% (144/274)
Abscess		
Paravertebral/epidural	18% (15/82)	62% (143/229)
Fistula	6 patients	
Diagnosis tuberculosis vertebra		
Bacteriological	0/82	62% (114/183)
Histological	55% (45/82)	72% (87/121)
Bacteriological and/or histological		50 patients (n = 58)
Tuberculosis elsewhere	10% (8/82)	27% (81/295)
Treatment		
Surgery	100% (82/82)	61% (181/295)
Chemotherapy		
IRP		10 patients
IRPE	35 patients	122
IRPS	21	38
IRE	26	29
RPE		2
IR(Z)(E)		42
Different combinations of IRPES		29
No. of deaths	0%	3% (8/245)
Reason TB		1
Radiological consolidation after 3–6 months	100% (82/82)	99% (72/73)
Treatment completed as planned	100% (82/82)	93% (227/245)
Cure rate no. of patients treatment completed	100%	100%
Follow-up in months after surgery, range	6–108	6–168
Follow-up completed as planned	100% (82/82)	96% (218/227)
Relapse	0% (0/56) (95%CI 0.0–6.4)	2% (4/218) (95%CI 0.6–5.0)

CI = confidence interval

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CHAPTER 5

INTRALESIONAL PENETRATION OF CHEMOTHERAPY IN TUBERCULOSIS

Penetration of isoniazid, rifampicin and pyrazinamide in tuberculous pleural effusion and psoas abscess

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ABSTRACT

There are no data on penetration of modern chemotherapy in tuberculous lesions. The intralesional concentrations of isoniazid (ISO), rifampicin (RIF) and pyrazinamide (PYR) in tuberculous pleural effusions and psoas abscesses were determined two hours after drug administration (six patients with pleural effusions, 10 patients with psoas abscesses). The measured levels were compared to reference serum values and minimal inhibitory concentration (MIC). This study was performed at the Tuberculosis Center Beatrixoord, University Medical Center Groningen, The Netherlands.

A similar range of concentrations was found for pleural effusions and psoas abscesses. Concentrations were below MIC values in none of 15 patients for ISO, in two of 13 for RIF, and in eight of nine for PYR. Cmax:MIC ratio (indicating effectiveness) was always > 4 for ISO, in four of 13 for RIF, and in none of 9 for PYR. In 5/8 patients receiving all three drugs both RIF and PYR had Cmax:MIC ratios < 4, indicating subtherapeutic drug levels.

It was concluded that penetration of ISO was always sufficient, of RIF mostly below the desired ratio, and for PYR on average 10 times too low. Five of eight patients on all three drugs had Cmax:MIC ratios < 4. This indicates intralesional subtherapeutic drug levels for RIF and PYR, and local monotherapy with ISO. This could induce drug resistance. Drainage as additional therapy seems indicated.

INTRODUCTION

The recommended treatment for almost all forms of tuberculosis (TB), is a short course regimen of isoniazid (ISO), rifampicin (RIF), pyrazinamide (PYR), and ethambutol (ETH) [1]. There are no separate guidelines for treatment of pleural effusions and psoas abscesses. Clinical results are generally good [1-5]. However, data on intralesional concentrations of these modern drugs are scarce. Insight into drug penetration is important since subtherapeutic drug concentrations may result in the selection of a resistant bacterial population and lead to treatment failure, e.g., chronic

tuberculous empyema. We investigated the concentrations of modern tuberculosis drugs (ISO, RIF, PYR) inside pleural effusions and abscesses.

MATERIALS AND METHODS

Patients with tuberculosis who were admitted to Tuberculosis Centre Beatrixoord, University Medical Centre Groningen, between June 1998 and December 2002 and who had a pleural effusion or a psoas abscess were included in the study. Each patient gave informed consent. Patients were treated with ISO, RIF, PYR and ETH. Specimens of serum (analysis of ISO), pleural effusion and psoas abscess fluid (analysis of ISO, RIF, and PYR) were taken by percutaneous drainage 2 h after administration of the drugs. ISO concentration in serum and pus was analysed directly with a spectrophotometric method according to Dymond and Russell [6].

For RIF and PYR concentrations, following immediate centrifugation, pleural effusion and abscess fluid were stored at -20°C until analysis by high performance liquid chromatography (HPLC). RIF and its metabolite desacetylrifampicin were both measured separately in plasma, or in pleural or abcess fluid, using straight phase HPLC with ultraviolet (UV) detection at 310 nm (or in case of interaction at 470 nm) (0.02 absorbance units full scale [AUFS]). The mobile phase was dichloromethane + isooctane + methanol + acetic acid 0.12% (36.6 + 45 + 16.8 + 1.4 v/v) at an isocratic flow of 1.5 ml/min. HPLC column was 150 x 3.0 mm inner diameter (ID) with silicagel Si-50 µm.

Five millilitres of plasma or centrifuged patient's pleural or abcess sample fluid + 50 µl methanol and 1.0 ml ascorbic buffer pH 6.0 (4 g ascorbic acid + 20 g sodium sulphate water free + 100 ml phosphate buffer 0.5 m at pH 6.0), were mixed and gently extracted by 1 ml of isooctane + dichloromethane (3 + 2 v/v) at room temperature. Exactly 90 ml of the extract was injected into the HPLC.

Limits of quantification (LOQ), recovery, coefficient of variation ($n = 6$) and linear correlation coefficient r of RIF in the sample were respectively 0.1 mg/l, 91%, 2.8%, and 0.9997, and for desacetylrifampicin they were 0.5 mg/l, 95%, 7.0% and 0.9983.

PYR was determined in plasma, pleural or abscess fluid, by using reversed phase HPLC with UV detection at 268 nm (0.1 AUFS). The mobile phase was potassium dihydrogenphosphate 0.067 M + methanol (82.5 + 17.5 v/v) + sufficient phosphoric acid to pH 5.5, at an isocratic flow of 1.0 ml/min. HPLC column was 150 x 4.6 mm ID with Nucleosil 5C18, 5 µm.

One millilitre of plasma or centrifuged patient's pleural or abscess sample fluid was added to 0.2 ml perchloric acid 5%, and vortex mixed for 30 seconds; 0.1 ml dipotassium hydrogenphosphate 4M was added and vortex mixed for 30 seconds and centrifuged for 5 min at 1500 g. Exactly 20 µl of the clear upper layer was injected into the HPLC. The metabolites hydroxypyrazinoic acid and pyrazinoic acid do not interfere with this method. The LOQ, recovery, coefficient of variation ($n = 6$) and linear correlation coefficient r of PYR in the sample were respectively 1 mg/l, 101 %, 1.7% (C 30 mg/l), and 0.9999.

The reference values and minimal inhibitory concentration (MIC) values for drug concentrations are shown in Table 1.

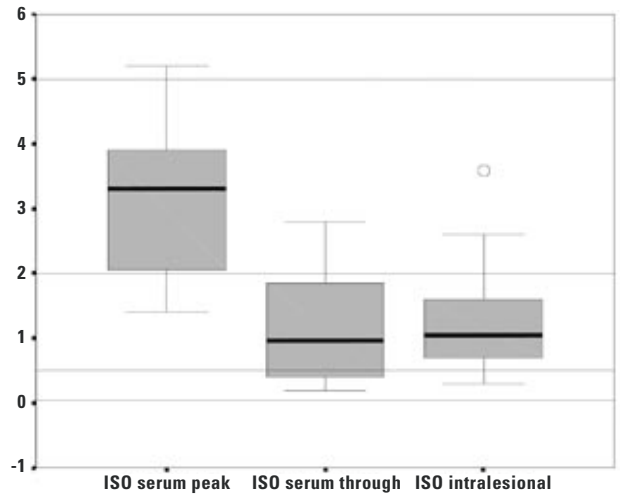
RESULTS

Participants in the study were six patients with a pleural effusion and 10 patients with a psoas abscess (Table 2). Drug regimens were not equal for all 16 patients. There were three Dutch, 10 African, and three Asian patients. Nationality, sex, and age were associated with different patterns of drug distribution. The measured concentrations of ISO, RIF, and PYR are shown in Table 3. The same range was found for pleural effusions and psoas abscesses.

Intralesional drug concentrations were below MIC values in 0/15 patients for ISO, in 2/13 for RIF, and in 8/9 for PYR. In 2/15 patients ISO levels reached reference serum peak values, 12/15 were equal to reference serum trough values and in 1/15

Figure 1

The various concentrations of isoniazid (ISO): serum peak, serum trough, and intralesional. Reference lines: lower line at minimal inhibitory concentration (MIC) for ISO: 0.05. Middle lines at serum trough reference values 0.5 to 2.0 and top line at 5.0 to indicate maximum serum peak reference value. Intralesional concentration in patient 2 was 3.6. Separately shown by o.

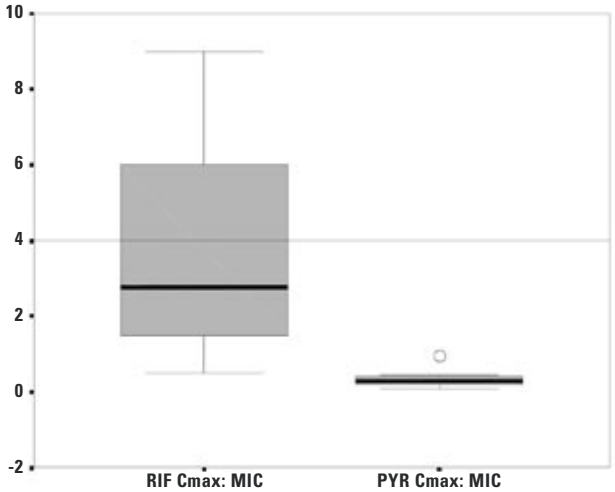


cases they were lower (Figure 1). In 3/13 patients RIF levels were higher than reference serum trough concentrations, in three cases equal, and in seven they were lower. In 2/9 patients PYR reached reference serum trough levels intralesionally, and for the other seven cases it was lower. According to Heifets, a rough measure of the potency of a drug is the ratio of the maximal concentration and the MIC (Cmax:MIC ratio). A ratio > 4 indicates probable effectiveness [7]. Cmax:MIC ratio was always greater than 4 for ISO, in 4 of 13 for RIF, and in none of 9 for PYR (Table 4, Figure 2).

All patients underwent drainage of their lesions. Patient number 3 died, 3 weeks after admission, due to progressive disease. On admission he was severely ill and extremely cachectic, with coexisting diabetes mellitus. Results were good in the other patients: at last follow-up none showed signs of a relapse (follow-up range 6 months to 3 years).

Figure 2

Cmax:MIC ratio for rifampicin (RIF) and pyrazinamide (PYR). Reference line drawn at 4.0 indicating probable effectiveness above this line[7]. Highest value for pyrazinamid was 1.45 for patient 1 indicated by o.



DISCUSSION

Levels of modern drugs ISO, RIF, and PYR were variable, but in the same range for pleural effusions and psoas abscesses. Intralesional drug concentrations were below MIC values in 0/15 patients for ISO, 2/13 for RIF, and 8/9 for PYR. The Cmax:MIC ratio was always >4 for ISO, in 4 of 13 for RIF, and in none of 9 for PYR. In five of eight patients receiving all 3 drugs, both RIF and PYR had Cmax:MIC ratios <4, indicating intralesional subtherapeutic drug levels. Chemotherapy and drainage cured all but one patient.

Given the limited number of patients and the varying constitution of drug treatment in this study, care must be taken in interpreting the results. Data of all three drugs were only available in eight of 16 patients. As drug levels for both pleural effusions and psoas abscesses were in the same range, it was considered useful to evaluate them together in this study. As substance entities are different, it is not known how this would influence the local drug effect.

There is a need for data on intralesional modern drug levels. Several in vitro studies have been done in the past [8-11]. In vitro measurements of drug activity predict the potency of a drug to prevent the emergence of resistance to other antimycobacterial drugs. They do not predict the sterilising activity of a drug or the activity of drug combinations. There are no data in the literature of PYR. Previous clinical investigations have concluded that the penetration of aminoglycosides, RIF and quinolones into the pleural space is likely to be good and short course chemotherapy is highly effective. However, drug concentrations were not measured [2,12]. In one study the concentrations of parenterally administered aminoglycosides were substantially lower in empyema than in sterile pleural fluid [13]. Intralesional subtherapeutic drug concentrations may occur in empyema, resulting in selection of a resistant bacterial population, and treatment failure [14-16].

On the other hand, four cases with a good penetration of streptomycin (STR) and ethambutol (ETH) in psoas abscesses were reported despite thickening of the walls during follow up [4]. Tuli found concentrations of STR and ETH in abscess fluid to be half to one third of the concentration in the serum. All values were much higher than those considered having an inhibitory effect on *Mycobacterium tuberculosis* in clinical material [5].

Explanations for the varying drug levels may be that concentrations are not homogenous throughout the lesions due to high viscosity and lack of intralesional flow. The variable thickness of the fibrous tissue surrounding the fluid collections may prohibit the penetration of drugs to a certain extent. Also binding or inactivation by material in the purulent fluid may occur [14-15].

A possible cause for low concentrations found for RIF and PYR, might be that drugs in pleural effusions and psoas abscesses reach peak levels several hours later than the standardised time interval of 2 h for peak and 6 h for trough levels in serum. In addition, a single sampling point does not take into account that different drugs have different distribution pharmacokinetics and may be distributed into lesions at different rates. Therefore, a single sampling point, cannot reflect a complete picture of intralesional levels for the different drugs. Time to maximal concentration in pleural fluid has been reported as long as 8 h later than in serum [14]. However, Wu et al. also

found low intralesional levels for RIF. Time after administration to reach these low peak levels was comparable to serum [17]. Nevertheless, observed differences with levels 2 h after drug administration were marginal in both reports. Further explanations could be varying pH, protein levels, glucose levels, and oxygen grade [8-11,14,18-20].

In five of eight patients receiving all three drugs, local subtherapeutic levels of both RIF and PYR were found. This means that only ISO reached intralesional therapeutic levels (local monotherapy). The old surgical saying "ubi pus evacua" applies here. Drainage in conjunction with antituberculosis drug treatment proved an effective, safe procedure in the treatment of tuberculous iliopsoas abscesses [21]. Randomised controlled trials of drainage could not be found in literature. Drainage reduces the intralesional bacterial load and is likely to shorten the time to resolution of the lesions. It may therefore reduce the risk of formation of drug-resistance due to local monotherapy. Drainage seems indicated as additional therapy for pleural effusions and psoas abscesses.

CONCLUSION

Intralesional drug concentrations of ISO, RIF, and PYR were variable. The same range was found for pleural effusions and psoas abscesses. Cmax:MIC ratio for ISO was always sufficient, for RIF in most cases below the desired ratio, and for PYR on average 10 times too low. In five of eight patients receiving all three drugs, both RIF and PYR had Cmax:MIC ratios <4, indicating intralesional subtherapeutic drug levels for RIF and PYR. The resulting local monotherapy with ISO may lead to the selection of a resistant bacterial population and treatment failure. Drainage as additional therapy seems indicated.

TABLES

Table 1
Reference values for concentrations in serum (mg/l).

Reference values mg/l serum	isoniazid (ISO)	rifampicin (RIF)	pyrazinamide (PYR)
Trough (8 hr)	0.5-2.0	0.5-1.0	10-30
Peak (2 hr)	2.0-5.0	8.0-24.0	30-50
Minimally inhibitory concentration (MIC)	0.05	0.2	20

Source: Dutch National Institute of Public Health and the Environment (RIVM)

Table 2
Patient characteristics.

Patient	Sex	Age	TB lesion	Drug resistance	HIV
1	F	33	Pleural effusion	Unknown	—
2	M	25	Pleural effusion	None	—
3	M	73	Pleural effusion	Unknown	—
4	F	21	Pleural effusion	None	+
5	F	33	Pleural effusion	None	—
6	M	70	Pleural effusion	None	—
7	M	63	Psoas abscess	None	—
8	M	28	Psoas abscess	Unknown	—
9	F	47	Psoas abscess	Unknown	—
10	F	38	Psoas abscess	Streptomycin	—
11	M	27	Psoas abscess	None	—
12	F	46	Psoas abscess	None	—
13	F	38	Psoas abscess	None	—
14	M	14	Psoas abscess	None	—
15	M	24	Psoas abscess	None	—
16	M	55	Psoas abscess	None	—

F = female; M = male; HIV = human immunodeficiency virus

Table 3

Administered dose in mg of isoniazid (ISO) and concentrations in mg/l of ISO, rifampicin (RIF), and pyrazinamide (PYR) in serum and pleural (1-6) or psoas abscess fluid (7-15).

Patient	Dose ISO mg	Serum ISO mg/l Peak	Trough	Intralesional ISO mg/l	Intralesional RIF mg/l	Intralesional PYR mg/l
1	300	1.9	1.1	1.7	-	29.0
2	250	5.2	2.8	3.6	0.3	-
3	300	-	-	0.9	0.7	2.0
4	300	2.6	0.6	0.5	0.9	4.0
5	400	1.4	0.2	2.6	1.2	-
6	250	3.2	-	0.8	0.3	8.0
7	300	1.7	-	1.4	0.2	-
8	300	3.6	1.0	0.8	1.8	6.4
9	300	4.8	0.4	1.4	-	-
10	300	4.6	2.3	-	0.1	-
11	300	3.4	2.0	1.5	0.5	19.0
12	300	1.6	0.3	0.9	1.5	4.0
13	300	4.0	0.4	0.6	0.4	9.0
14	300	3.2	1.7	0.3	0.3	5.0
15	300	3.8	2.2	1.2	-	-
16	300	2.2	0.9	0.9	0.3	-

Table 4

The ratio of the maximum concentration compared to the minimal inhibitory concentration (Cmax:MIC ratio) of isoniazid (ISO), rifampicin (RIF), and pyrazinamid (PYR) in pleural (1-6) or psoas abscess fluid (7-15).
A Cmax:MIC ratio >4 indicates probable effectiveness[7].

Patient	Cmax:MIC ratio ISO	Cmax:MIC ratio RIF	Cmax:MIC ratio PYR
1	34	-	1.45
2	72	1.5	-
3	18	3.5	0.1
4	10	4.5	0.2
5	52	6.0	-
6	16	1.5	0.4
7	28	1.0	-
8	16	9.0	0.32
9	28	-	-
10	-	0.5	-
11	30	0.5	0.95
12	18	7.5	0.2
13	12	2.0	0.45
14	6	1.5	0.25
15	24	-	-
16	18	1.5	-

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CHAPTER 6

ROUTINE SURGERY IN THE TREATMENT OF SPINAL TUBERCULOSIS

Routine surgery in addition to chemotherapy for treating spinal tuberculosis (Review)

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ABSTRACT

Background

Tuberculosis is generally curable with chemotherapy, but there is controversy in the literature about the need for surgical intervention in the one to two per cent of people with tuberculosis of the spine.

Objectives

To compare chemotherapy plus surgery with chemotherapy alone for treating people diagnosed with active tuberculosis of the spine.

Search strategy

We searched the Cochrane Infectious Diseases Group Specialized Register (October 2005), CENTRAL (*The Cochrane Library* 2005, Issue 4), MEDLINE (1966 to October 2005), EMBASE (1974 to October 2005), LILACS (1982 to October 2005), conference proceedings, and reference lists.

Selection criteria

Randomized controlled trials with at least one year follow up that compared chemotherapy plus surgery with chemotherapy alone for treating active tuberculosis of the thoracic and/or lumbar spine.

Data collection & analysis

Two authors independently assessed trial eligibility, methodological quality, and extracted data. We analysed data using odds ratio with 95% confidence intervals.

Main results

Two randomized controlled trials (331 participants) met the inclusion criteria. They were conducted in the 1970s and 1980s with follow-up reports available after 18 months, three years, and five years; one trial also reported 10 years follow up. Completeness of follow up varied at the different time points, with less than 80% of participants available for analysis at several time points. There was no statistically

significant difference for any of the outcome measures: kyphosis angle, neurological deficit (none went on to develop this), bony fusion, absence of spinal tuberculosis, death from any cause, activity level regained, change of allocated treatment, or bone loss. Neither trial reported on pain. Of the 130 participants allocated to chemotherapy only, 12 had a neurological deficit and five needed a decompression operation. One trial suggested that an initial kyphosis angle greater than 30° is likely to deteriorate, especially in children.

Reviewers' conclusions

The two included trials had too few participants to be able to say whether routine surgery might help. Although current medication and operative techniques are now far more advanced, these results indicate that routine surgery cannot be recommended unless within the context of a large, well-conducted randomized controlled trial. Clinicians may judge that surgery may be clinically indicated in some groups of patients. Future studies need to address these topics as well as the patient's view of their disease and treatment.

PLAIN LANGUAGE SUMMARY

Not enough evidence on the routine use of surgery in addition to drug treatment for people with tuberculosis of the spine.

Spinal tuberculosis (spinal TB) occurs in about 1% to 2% of people with TB (the most common infectious disease in the world). The disease can have a major impact on people's lives. Nerves can be squeezed causing pain, loss of feeling, and breathing problems. It can cause bone loss and curvature of the spine, which can lead to loss of nerve function and paralysis after some years, even if the TB has been cured. Correcting with surgery at this point can be difficult because of the complexity of the surgery required. It has been suggested that surgery might be undertaken at the time the TB of the spine is diagnosed and drug treatment (chemotherapy) is being used. However, all surgery has potential adverse effects. This review of trials found there were insufficient numbers of participants in the two trials located (331 participants) to be able to say if routine surgery early on was of overall benefit. Further trials are needed and such trials should assess the pain that people suffer and their views of the disease and treatment.

BACKGROUND

Incidence

Tuberculosis is the most common infectious disease in the world. Every year 10 million new people are infected (WHO 2005). While tuberculosis commonly infects the lungs, it is located in the spine in one to two per cent of people (Watts 1996).

Pathology

Tuberculosis of the spine is potentially serious. The infection can cause pain and destroy the bone making the vertebral bodies collapse, thereby flexing the spine forward (kyphosis) (Figure 01). Sometimes a nerve root may be compressed causing pain along the root or deficit, but more commonly spinal cord compression may lead to myelopathy (loss of feeling and muscle control) or paraplegia. Even lung function may be compromised (Smith 1996). If there is a sharp angle in the spine due to bony destruction, loss of neurological function may manifest only after years, even if the tuberculosis has been cured adequately (Hsu 1988; Rajeswari 1997a; Luk 1999). This is the result of chronic compression of the spinal cord or a local reactivation. Late paraplegia due to spinal cord compression is a major problem because an operation at this stage is complex and prone to major complications often without subsidence of the neurological deficit (Moon 1997). If the bone has fully fused in a normal position after the primary illness period, this late consequence is thought not to occur (Leong 1993).

Most experts believe that a kyphosis over 30° is likely to generate back pain and to deteriorate (Kaplan 1952; Rajeswari 1997b; Wimmer 1997; Parthasarathy 1999 (see ICMR/MRC 1989)). Vertebral body bone loss is a measure of destruction of the bone as seen on lateral radiographs. It is expressed as units (U), 1.0 U meaning a complete vertebral body and 0.0 U meaning no bone loss; for example, if two bodies are partially destroyed, one lost 50% of its volume and the other 25%, the bone loss is 0.75 U. It has been claimed to predict the final kyphosis angle (Rajasekaran 1987).

Diagnosis

Diagnosis of spinal tuberculosis in endemic areas is made mainly using radiographs. Active disease is diagnosed when there is loss of the thin cortical outline and rarefaction of the affected vertebral bodies (MRC 1974a). Ideally there is a positive culture from the site of the lesion.

Treatment

Tuberculosis in general is curable. The mainstay of treatment is chemotherapy with at least isoniazid, rifampicin, and pyrazinamide. The American Thoracic Society recommends six months of chemotherapy for spinal tuberculosis in adults and 12 months in children because reliable data are lacking on shorter treatment duration (Bass 1994). The British Thoracic Society recommends six months of treatment irrespective of age (BTS 1998). In their recent review of the literature, Van Loenhout-Rooyackers and colleagues found that six months of treatment is probably sufficient for everyone (Van Loenhout 2002).

Goals of treatment

In tuberculosis, treatment is considered to be successful when the person is cured, is no longer infectious, and does not suffer relapse. However, some additional unique problems are encountered in spinal tuberculosis, namely, kyphosis angle and neurological deficit. Treatment in spinal tuberculosis is directed toward controlling or correcting the kyphosis angle thereby restoring the balance of the spine, restoring normal neurology, preventing pain, achieving early bony fusion (healing), preventing local recurrence of spinal tuberculosis, and preventing bone loss. Furthermore, people need to regain their previous activity level to enable them to resume their normal lives, school, jobs, and sports.

Human immunodeficiency virus (HIV) increases the risk of reactivation of a latent focus and progression of the disease to a more atypical and severe course. Studies directed specifically at spinal tuberculosis and HIV conclude that good clinical outcomes can be expected irrespective of the HIV status and the availability of antiretroviral therapy (Leibert 1996; Govender 2000). Another report mentions that people with HIV are not a homogeneous group, and that results – especially complications like wound infections – worsen during the end stage of the disease (Jellis 1996).

Role of surgery

There is controversy in the literature about the necessity of additional surgical intervention to spinal tuberculosis treatments. This difference of opinion goes back to 1960 when Hodgson and Stock advocated surgical treatment (Hodgson 1960), and Konstam and colleagues advocated conservative treatment (Konstam 1958; Konstam 1962). Conservative treatment consists of only medication and sometimes additional non-operative measures (physical therapy, orthosis, and bed rest). Surgery can basically be divided into two procedures. The first is a debridement. This is a procedure that comprises surgical removal of the infected material. No attempt is made at stabilizing the spine. The second form, which is more extensive, is a debridement with stabilization of the spine (spinal reconstruction). The reconstruction has always been performed with bone grafts. Today, countries with sufficient resources perform stabilization using artificial materials like steel, carbon fibre, or titanium (instrumentation).

Although randomized controlled trials investigating indications are lacking, many authors consider the following indications for surgical intervention: (1) neurological deficits (with an acute or non-acute onset) caused by compression of the spinal cord; (2) spinal instability caused by destruction or collapse of the vertebrae, destruction of two or more vertebrae, or kyphosis of more than 30°; (3) no response to chemotherapeutic treatment; (4) non-diagnostic biopsy; and (5) large paraspinal abscesses (Vidyasagar 1994; Chen 1995; Nussbaum 1995; Rezai 1995; Boachie-Adjei 1996; Watts 1996; Moon 1997). Some authors even advocate surgery in mild cases of spinal tuberculosis (Leong 1993; Luk 1999; Turgut 2001).

Potential benefits of surgery are less kyphosis, immediate relief of compressed neural tissue, quicker relief of pain, a higher percentage of bony fusion, quicker bony fusion, less relapse, earlier return to previous activities, and less bone loss. It may also prevent late neurological problems due to kyphosis of the spine if fusion has not occurred (Hsu 1988; Leong 1993).

Surgery requires expertise, good anaesthesia, and excellent peri-operative care. It also requires hospitalization, and is expensive and potentially dangerous. Complications can occur during the operation or postoperatively. Complications of spinal surgery can be divided into several groups: reconstruction-related, vascular, neurological, visceral, and wound-related. Reconstruction failures can be breakage of the graft, screws and rods, loss of correction, and failure of fusion (Jutte 2002). Vascular problems during surgery can be massive bleeding, haematoma formation, and thromboembolism. Neurological damage of surgery can be nerve root lesion, dura tears, spinal cord infarction, and plexus lesions. Visceral damage, especially ureteric lesions, can occur. Wound infections happen in 1% to 6% of spinal surgeries (Fardon 2002). Considering the potential complication rate, surgery should only be performed if there is a clear benefit.

OBJECTIVES

To compare chemotherapy plus surgery with chemotherapy alone for treating people diagnosed with active tuberculosis of the spine.

CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

Types of studies

Randomized controlled trials with at least one year follow up after the start of treatment.

Types of participants

People diagnosed with active tuberculosis of the thoracic and/or lumbar spine, including the upper sacral vertebra S1 (Figure 02).
Active disease is diagnosed on the radiographs; there is loss of the thin cortical outline and rarefaction of the affected vertebral bodies (MRC 1973a).

Types of interventions

Intervention
Chemotherapy plus surgery.

Control
Chemotherapy.

Both the intervention and control group must have received comparable adequate chemotherapy regimen of at least six months. Adequate refers to the guidelines commonly used when the trial took place.

Types of outcome measures
We assessed all outcome parameters reported at any follow-up time.

Primary
- Kyphosis angle.
- Neurological deficit.

Secondary
- Pain.
- Bony fusion, defined as the healing of adjacent affected vertebral bodies. There is continuity of trabeculae (bone bars) between the vertebral bodies and/or stout bony bridges, usually best seen in the anteroposterior radiograph, projecting up to 2 cm wide of the vertebral bodies and showing trabecular continuity even though the vertebrae are still separated by a small space, often no more than a hairline.
- Absence of spinal tuberculosis.
- Deaths from any cause.
- Regained activity level, defined as the number of participants that regained their previous activity level, which is the ability of people to resume their normal lives, do their previous jobs, sports, etc.
- Bone loss, defined as a measure of destruction of the bone as seen on lateral radiographs. It is expressed as units (U), 1.0 U being loss of a complete vertebral body and 0.0 U being no bone loss; for example, if two bodies are partially destroyed, one lost 50% of its volume and the other 25%, the bone loss is 0.75 U.

Adverse events
Events related or probably related to the treatment having a negative effect on the well-being of the participants other than death (reported separately); this includes surgical complications, failure of reconstruction, paraplegia from the operation, and adverse effects of medication.

SEARCH STRATEGY FOR IDENTIFICATION OF STUDIES

We attempted to identify all relevant trials regardless of language or publication status (published, unpublished, in press, and in progress).

Databases
We searched the following databases using the search terms and strategy described in Table 01.
- Cochrane Infectious Diseases Group Specialized Register (October 2005).
- Cochrane Central Register of Controlled Trials (CENTRAL), published in *The Cochrane Library* (2005, Issue 4).
- MEDLINE (1966 to October 2005).
- EMBASE (1974 to October 2005).
- LILACS (1982 to October 2005).

Reference lists
We also checked the reference lists of all studies identified by the above methods.

METHODS OF THE REVIEW

Trial selection
We scanned the results of the literature search for potentially relevant trials and retrieved their full articles. We independently assessed the potentially relevant trials for inclusion in the review using an eligibility form based on the inclusion criteria. We ensured each trial was included only once and resolved disagreements through discussion. The excluded studies are listed together with the reason for excluding them in the 'Characteristics of excluded studies'.

Assessment of methodological quality
We independently assessed the methods used to generate the allocation sequence and conceal allocation as adequate, inadequate, or unclear according to Jüni 2001. We also assessed the inclusion of all randomized participants in the final analysis and considered at least 80% completeness of follow up at each time point to be adequate. Blinding of the treating physicians was not possible at the time of treatment or at follow up. Blinding of the assessor of the radiographs of both trials was limited to pre-treatment investigations. At follow up, no information of the treatment given was provided; signs can frequently be seen on radiographs after an operation, especially

after a reconstruction with a bone graft. We resolved any disagreements through discussion.

Data extraction

The first author extracted the data using a data extraction form and entered the data into Review Manager 4.2. The second author cross checked the data with the original paper. We also extracted the number of participants allocated to surgery who were not operated on, and those allocated to chemotherapy alone who received surgery. We resolved disagreements by referring to the original paper.

Data on neurology, pain, bony fusion, absence of spinal tuberculosis, death from any cause, activity level, and change of allocated treatment were handled as dichotomous data. Data on angle of kyphosis can be handled as continuous or dichotomous. Continuous was preferred, but the required data on standard deviation were not provided. We handled the data as dichotomous data in two ways: (a) a final kyphosis angle being ≤ 30° or > 30°; and (b) a progression ≤ 10° or > 10°.

Data analysis

We analysed the data using Review Manager 4.2. We used odds ratio (OR) to assess all dichotomous outcome measures. We used the fixed-effect model and presented the data with 95% confidence intervals (CI).

DESCRIPTION OF STUDIES

Search results

The search strategy revealed 25 potentially relevant papers; their reference lists revealed another three. We studied the full-text versions of all 28 papers. We excluded 21 papers (*see* 'Characteristics of excluded studies') and included seven publications reporting on two randomized controlled trials involving 331 participants (*see* 'Characteristics of included studies').

The British Medical Research Council Working Party on Tuberculosis of the Spine (MRC) co-ordinated both randomized controlled trials, one in co-operation with the Indian Council of Medical Research (ICMR). The MRC performed a series of randomized controlled trials investigating the varying ways of treatment of tuberculosis of the spine in several centres. This review includes two of these trials: one from Bulawayo, Rhodesia (now Zimbabwe) (MRC 1974a); and the other from Madras, India (ICMR/MRC 1989).

The different publications reported on the trials after 18 months, three years, and five years (MRC 1974a; ICMR/MRC 1989); ICMR/MRC 1989 also reported 10 years follow up. The results at five years for ICMR/MRC 1989 were described in three different papers. We used an article published by the MRC in 1999 to assess the five year follow up of ICMR/MRC 1989 as it is the official report of the trial and provides the most detailed information of all three.

Participants

We have detailed the inclusion and exclusion criteria in the 'Characteristics of included studies' and summarized the characteristics of the 331 enrolled and randomized participants in Table 02. Trials reported on the number of participants evaluable at the various times of follow up (Figure 03 and Figure 04). Both trials included children (less than 15 years old) and adults, men and women. The location of the spinal lesion was thoracic (T1 to T10), thoracolumbar (T11 to L2), and/or lumbosacral (L2 to S1) (Figure 02). A few participants had neurological deficit on entry but all were able to walk.

Interventions

MRC 1974a randomized 130 people to chemotherapy plus surgical debridement (no reconstruction) or chemotherapy alone. All participants received p-amino salicylic acid (PAS) and isoniazid for 18 months. Half of them were randomized to receive streptomycin as extra in the first three months. We were unable to determine exactly which individual participants received streptomycin, but for the purpose of this review we did not consider this a reason for exclusion. Streptomycin is not a potent drug in the treatment of tuberculosis and is no longer part of the recommended treatment regimen (Bass 1994; BTS 1998).

ICMR/MRC 1989 randomized 201 participants to chemotherapy plus surgery (debridement and reconstruction with bone graft) or to chemotherapy alone. The chemotherapy for all participants was a six-month regimen of isoniazid and rifampicin. The trial also included a third arm, which we had to exclude because these participants received a different chemotherapy regimen consisting of nine months treatment.

Outcomes

The trials reported on all the prespecified outcome measures except pain.

METHODOLOGICAL QUALITY OF INCLUDED STUDIES

See 'Methods of the review' for details and a summary of the quality assessment in Table 03.

The methods used to generate the allocation sequence were unclear in both trials, but the concealment of allocation was adequate. Completeness of follow up in the MRC 1974a trial was inadequate after three years (72%) and five years (62%). In the ICMR/MRC 1989 trial, it was adequate at three years (83%) and five years (82%), but inadequate at 10 years (78%).

Analysis in the two trials appeared to be by intention to treat. In the chemotherapy group across the two trials, 12 participants had neurological complications at entry to the trial: five of these required surgery. Details on reasons behind the change of allocated treatment are given in Table 04. In the chemotherapy plus surgery group across the two trials, there was a problem with exposure of the bone during operation in two participants and the procedure was abandoned: both were treated with chemotherapy only. We looked for a difference in the numbers of participants where their actual treatment group was different to what they were originally randomized to and detected no difference (*comparison 01-01*).

Kyphosis angle

Both trials reported on kyphosis angle. They used two methods to report change in the angle.

Mean increase of kyphosis angle (progression of kyphosis angle at follow up)

Both trials reported that the mean degree of kyphosis angle was within the same range at 18 months, three years, five years, and 10 years (Table 05), but we were unable to assess statistical significance because standard deviations were not provided.

In ICMR/MRC 1989 at 10 years follow up, a kyphosis of greater than 30° at the start of treatment deteriorated (increased) with a mean of 10° to 30°. The investigators describe a subgroup effect for age on kyphosis angle for the chemotherapy group: 17 participants younger than 15 years with an initial angle greater than 30° had a mean deterioration of 30° compared with the same treatment in 13 participants older than 15 years with angles greater than 30° who deteriorated with a mean of 10° (P = 0.001).

Kyphosis angle: > 10° deterioration

MRC 1974a measured this at five years (65 participants) for lesions in the thoracic, thoracolumbar, and lumbosacral areas (T1 to S1), and ICMR/MRC 1989 measured this at three years (78 participants) and five years (79 participants) for lesions in the thoracic and thoracolumbar areas (T1 to L2). There was no statistically significant difference between groups at three years (78 participants, 1 trial) or five years (144 participants, 2 trials); *comparison 01-02*.

Neurological deficit

Both sets of trials reported on the neurological status of the participants. No participants without neurological deficit on entry developed neurological deficit. Neurological deficit was present at entry in 23 participants and there was no statistically significant difference at 18 months (23 participants, 2 trials), three years (23 participants, 2 trials), five years (20 participants, 2 trials), and 10 years (10 participants, 1 trial); *comparison 01-03*.

Pain

Neither trial reported on pain.

Bony fusion

There was no statistically significant difference between chemotherapy plus surgery and chemotherapy alone on the presence of bony fusion at 18 months (256 participants, 2 trials), three years (247 participants, 2 trials), five years (236 participants, 2 trials), or 10 years (156 participants, 1 trial); *comparison 01-04*.

Absence of spinal tuberculosis

There was no statistically significant difference between the intervention and control at 18 months (261 participants, 2 trials), three years (262 participants, 2 trials), five years (244 participants, 2 trials), and 10 years (156 participants, 1 trial); *comparison 01-05*.

Deaths from any cause

Both sets of trials reported on deaths from any cause (details provided in Table 06). There was no statistically significant difference between the groups at 18 months (262 participants, 2 trials) or three years (262 participants, 2 trials); *comparison 01-06*. Follow up at five or 10 years was impossible to assess because details on which patient died in which group were not provided.

Regained activity level

Both sets of trials reported on activity level, but neither provided data on the participants' activity levels when they entered the trials. Around 90% of participants in both groups had reached their previous level of activity at 18 months follow up. One of the prerequisites for regaining activity level is normal neurology. There were no statistically significant differences between the groups at 18 months (262 participants, 2 trials), three years (262 participants, 2 trials), five years (244 participants, 2 trials), or 10 years (156 participants, 1 trial); *comparison 01-07*.

Bone loss

The trials used two methods of reporting data on bone loss.

Mean change of bone loss (mean difference between loss at entry and at follow up)

Neither trial report included standard deviations, which meant that we were unable to

assess the statistical significance of the data on the mean bone losses. The major bone loss (vertebral destruction) was present at the time of diagnosis; only limited further destruction occurred during treatment and the subsequent follow-up period (*see* Table 07).

Large change in bone loss

An unwanted result is considered when the amount of bone loss has deteriorated greater than 0.25 U. MRC 1974a reported on this at five years (58 participants), and ICMR/MRC 1989 reported data at three years (161 participants) and five years (150 participants). There was no statistically significant difference at three years (161 participants, 1 trial) or five years (220 participants, 2 trials); *comparison 01-08*.

Adverse events

Adverse events were defined as events related or probably related to the treatment having a negative effect on the well-being of the participants other than death (reported separately). Adverse events were not specifically reported by the trial authors, so we analysed the text to identify them (Table 08). One participant was operated on the wrong localization, there were seven graft failures (breakage and displacement), and 28 cases of hepatitis, a side effect of the chemotherapy.

DISCUSSION

The objective of this systematic review was to compare chemotherapy plus surgery with chemotherapy alone for treating people diagnosed with active tuberculosis of the thoracic and/or lumbar spine. No statistically significant benefit of routine surgery was found. Most participants received the treatment of the group to which they were allocated. Reasons for changing treatment were mainly neurological: five of 12 participants from the chemotherapy group had surgery because of persisting or deteriorating neurological deficit. Participants with neurological deficit form an interesting subgroup for further studies.

Effects on the spine

The review did not demonstrate an effect of surgery on the kyphosis angle. The incidence of progressive kyphosis was high for all participants, as was the kyphosis angle at the start of either treatment. Many spine surgeons nowadays consider a kyphosis greater than 30° to be unacceptably high and an indication for operative correction in the first place (Vidyasagar 1994; Chen 1995; Nussbaum 1995; Rezai 1995; Boachie-Adjei 1996; Watts 1996; Moon 1997). Nor did the review show a difference with respect to bony fusion, often considered the best evidence of healing (MRC 1974a). Further deterioration of the kyphosis angle is unlikely after fusion.

There was no statistically significant difference between the two intervention groups on the presence of bony fusion at any reported follow up. Data on the speed of bony fusion were not provided in either trial, so differences during early phases of treatment could not be assessed. Over time, bony fusion is obtained in a high percentage of participants regardless of the way of treatment. Similarly, bone loss was not influenced by treatment group. The amount of bone is considered important for the stability of the spine. People with a total bone loss of more than three U were excluded, and the role of surgery in these more severe cases could not be assessed.

Neurological deficit and mobility

A small number of participants had a neurological deficit at entry, and there were no statistically significant differences between the interventions in the improvement of this deficit. Deterioration of neurological deficit or persisting deficit with spinal cord compression can be an indication for surgery (Martini 1976; Leong 1993; Watts 1996; Moon 1997). There was a subgroup of 12 participants from the chemotherapy only group (130) with neurological deficit on entry; five of these 12 needed an operation to decompress the spinal cord.

Two studies reporting on non-surgical treatment of spinal tuberculosis conclude that it is successful in the majority of cases, even in the presence of neurological deficit (Pattison 1986; Nene 2005). However, the participants were not randomized, one of the studies was retrospective (Nene 2005), and the follow up was 25% at five years for the other report (Pattison 1986).

Some authors advocate the so-called 'middle path regimen' in which only patients with neurological deficit have operations (Tuli 1975; Jain 2004). They report good results, but there are no trials comparing this regimen to purely non-surgical treatment or routine surgical treatment. None of the participants included in the included trials were paralysed severely enough to prevent them from walking across a room. Therefore the role of surgery in these more severe cases could not be assessed.

Almost all participants reached their previous activity levels at first follow up, regardless of treatment. However, data on activity level on entry of the study were not provided, so the actual improvement could not be assessed. Furthermore, there may have been differences in the speed of recovery. Regrettably neither trial assessed this.

Deaths and adverse events

There was no statistically significant difference in the number of deaths from any cause at 18 months or three years follow up. Because the trials did not provide details, we were unable to assess the mortality at five or 10 years. In ICMR/MRC 1989, four participants died as a consequence of surgical procedures. The procedure was introduced to the orthopaedic centre for this particular trial. Because of these deaths, the investigators concluded that there are problems in introducing a new

major surgical procedure, even in an orthopaedic centre, and suggest that in the light of the excellent results achieved by chemotherapy alone that this procedure need not and should not be introduced (ICMR/MRC 1989). The operations with their high mortality rate (4/85) were performed between 1975 and 1978. Perioperative care has improved since, and no deaths have been reported from more recent series of operations (Güven 1994; Rezai 1995; Lee 1999; Turgut 2001; Sundararaj 2003).

Most adverse events were related to surgery. In ICMR/MRC 1989, four people died due to complications related to surgery, some of these are preventable with modern day knowledge. There were several problems related to the bone graft. The same trial reported that three or more disc spaces had to be spanned in seven participants with a kyphosis greater than 30°. All seven bone grafts failed (breakage or displacement) and the deformity progressed. Modern spinal instrumentation might prevent this failure.

There were no participants reported with cardio-respiratory failure related to the deformity. In neither series there were participants with late paraplegia in spite of some severe deformities. Follow up of 10 years might not be sufficient for this late paraplegia; it may only manifest itself after more than 15 years (Seddon 1935; Hsu 1988; Leong 1993; Luk 1999).

Limitations of the review

Follow up was inadequate for MRC 1974a at any time point and for 10 years follow up of ICMR/MRC 1989. In both sets of trials different techniques of surgery were used: debridement surgery (MRC 1974a) and debridement plus reconstruction with bone graft (ICMR/MRC 1989). As shown in the meta-analyses, there were no statistically significant differences between these techniques. Both sets of trials were performed many years ago, between 1964 and 1969 for MRC 1974a and between 1975 and 1978 for ICMR/MRC 1989. In recent years, new medications and better operative techniques have been developed.

The introduction of pyrazinamide in 1978 dropped the relapse rates for pulmonary tuberculosis from 7.8% and 20.3% to 1.4% and 3.4% after two and five years follow up, respectively (MRC 1987). Randomized controlled trials are needed to assess this newer medication in spinal tuberculosis.

Better techniques for correcting deformities of the spine like kyphosis and scoliosis are continually being developed. These techniques using metal or titanium screws, plates, and rods (instrumentation) have reported to be good at maintaining this correction (Güven 1994; Moon 1995; Rajasekaran 1998; Lee 1999; Özdemir 2003; Sundararaj 2003). However, no randomized controlled trials have been performed comparing chemotherapy alone with chemotherapy plus surgical instrumentation, and they are unlikely to be conducted because the main debate in spinal surgery is now whether the instrumentation should be anterior, posterior, or both (Güven 1994; Moon 1995; Moon 1997; Rajasekaran 1998; Özdemir 2003; Sundararaj 2003).

Another limitation of the review is that there were no data on how the patients found their treatment. It would be helpful if future studies also address this point.

REVIEWERS' CONCLUSIONS

Implications for practice

Two trials evaluated routine surgery in spinal tuberculosis, but data are insufficient to be clear whether this policy is better than chemotherapy alone (with surgery used when clinically indicated). These trials were performed some years ago, and current medication and operative techniques are far more advanced. However, these results indicate that routine surgery cannot be recommended unless within the context of a large, well-conducted randomized controlled trial.

Clinicians may judge that surgery may be indicated in subgroups of patients – with an initial kyphosis angle greater than 30° (especially in children) or progressive or persistent neurological deficit with spinal cord compression despite chemotherapy – but there are no randomized comparisons to support this.

Implications for research

Future trials need to assess routine surgery and also address subgroups of patients with spinal tuberculosis to establish the role of surgery for specific indications. These trials need to be large enough to assess outcomes properly. They need to assess pain and the patient's view of their disease and treatment.

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Potential conflict of interest

None known.

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Characteristics of included studies

Study	Methods	Participants	Interventions	Outcomes	Notes	Allocation concealment
MRC 1974a	Randomized controlled trial Generation of allocation sequence: unclear Allocation concealment: sealed envelopes Blinding: assessor only Inclusion of all randomized (enrolled) participants in the final analysis for primary outcomes: 1. Deformity: 73/130 (56%) at 3 years (73/94 available as x-rays technically inadequate or x-ray series incomplete for 21 participants); 65/130 (50%) at 5 years (15 participants not assessed for x-rays not being available on 0 or 60 months follow up) 2. Neurology: 68% (89/130) at 3 years; 62% (80/130) at 5 years; 5 participants excluded for neurological assessment (2 died of nontuberculous causes and 3 defaulted, all after 18 months) Length of follow up: 5 years, with assessment at 18 months, 3 years, and 5 years	Number*: 130 enrolled and randomized 94 available for analysis at 3 years, 36 lost to follow up due to no evidence on radiographs of tuberculosis (5), permanent default (6), excessive interruption (17), major drug change (3 toxicity, 1 brucellosis), death nontuberculous cause (3), admitted in error 1) 80 available for analysis at 5 years, 50 lost to follow up due to earlier exclusion (36 at 3 years), defaulted from follow up between 3 and 5 years (6), died of unrelated cause (3), not explained (5) Inclusion criteria: presence of clinical and radiographic evidence of tuberculosis of any vertebral body from the first thoracic to the first sacral, inclusive, that is excluding cervical and sacral disease; disease was active clinically and/or radiographically (radiographic active disease: (a) loss of the thin cortical outline and (b) rarefaction of the affected vertebral bodies); availability for observation over a period of 3 years Exclusion criteria: paraplegia or paraparesis severe enough to prevent walking; active tuberculosis in a lower limb requiring rest in bed; pulmonary tuberculosis of a type considered likely to complicate the management; a history of previous antituberculosis chemotherapy for 12 months or more; serious nontuberculous disease likely to prejudice the response to treatment or its assessment; a contraindication to the methods of the treatment under comparison	1. Chemotherapy Adults (>= 45 kg): daily streptomycin sulphate (1 g) by intramuscular injection for the first 3 months plus isoniazid (300 mg) and sodium PAS (10 g), both for 18 months Children (< 15 years) and adults (< 45 kg): daily streptomycin sulphate (20 mg/kg bodyweight) by intramuscular injection for the first 3 months plus isoniazid (6 mg/kg bodyweight; maximum 300 mg) and sodium PAS (0.2 mg/kg bodyweight; maximum 10 g), both for 18 months Participants randomized to this regimen or the same regimen without the initial 3 months of streptomycin 2. Chemotherapy plus debridement surgery Same chemotherapy regimen with debridement surgery: an operation to remove all necrotic and diseased tissue without reconstruction	1. Kyphosis angle 2. Neurological deficit 3. Bony fusion 4. Absence of spinal tuberculosis 5. Deaths from any cause 6. Regained activity level 7. Change of allocated treatment	Location: Bulawayo, Rhodesia (now Zimbabwe) Date: 3-year follow up in 1974; 5-year follow up in 1978 The 5-year report contains information about a study from Hong Kong performed by the same group of investigators, the British Medical Research Council (MRC), with the same criteria; we excluded this part of the report from the analysis because participants were not randomized between chemotherapy or chemotherapy plus surgery	A
ICMR/ MRC 1989	Randomized controlled trial Generation of allocation sequence: unclear Allocation concealment: sealed envelopes Blinding: assessor only Inclusion of all randomized (enrolled) participants in the final analysis for primary outcomes: 1. Deformity: 39% (79/201) at 5 years; 34% (69/201) at 10 years; not available at 3 years; lumbar lesions excluded for deformity measurements, so total number less than 201, and, as a consequence, the percentages are higher than 39% and 34%, but exact figures cannot be reconstructed from article 2. Neurology: 80% (161/201) at 5 years; 78% (156/201) at 10 years; not available at 3 years Length of follow up: 10 years, with assessment at 18 months, and 3, 5, and 10 years	Number*: 201 enrolled and randomized 168 available for analysis at 3 years; losses to follow up due to no tuberculosis (3), refused surgery (2), considered unfit for the anaesthetic (1), considered unfit for surgery (3), no evidence of active spinal tuberculosis on radiographs (7), defaulted from 4 to 25 months (1), died of nontuberculous causes (6), operated at wrong level (1), missed considerable amount (> 6 weeks) of chemotherapy (9) 164 available for analysis at 5 years; losses to follow up due to reasons detailed above (33), excluded due to death of unrelated cause, default, or additional chemotherapy due to tuberculosis in other location (4; no details given) 156 available for analysis at 10 years; losses to follow up due to reasons detailed above during 0 to 5 years (37), and excluded for nontuberculous death (4) or default from follow up (4) Inclusion criteria: presence of clinical and radiographic evidence of tuberculosis of any vertebral body from the first thoracic to the first sacral, inclusive, that is excluding cervical and sacral disease; disease was active clinically and/or radiographically (radiographic active disease: (a) loss of the thin cortical outline and (b) rarefaction of the affected vertebral bodies); availability for observation over a period of 3 years Exclusion criteria: paraplegia or paraparesis severe enough to prevent walking; active tuberculosis in a lower limb requiring rest in bed; pulmonary tuberculosis of a type considered likely to complicate the management; history of previous antituberculosis chemotherapy for 12 months or more; serious nontuberculous disease likely to prejudice the response to treatment or its assessment; contraindication to the methods of the treatment under comparison	1. Chemotherapy Isoniazid plus rifampicin (1 dose daily for 6 months) 2. Chemotherapy plus surgery Isoniazid plus rifampicin (1 dose daily for 6 months) with an operation consisting of debridement (removal of all necrotic and diseased tissue) and stabilization with a bone graft (reconstruction) Not included in review because it has a different chemotherapy regimen without a comparable surgical intervention group: 3. Chemotherapy Isoniazid plus rifampicin (1 dose daily for 9 months)	1. Kyphosis angle 2. Neurological deficit 3. Bony fusion 4. Absence of spinal tuberculosis 5. Deaths from any cause 6. Regained activity level 7. Change of allocated treatment	Location: Madras, India Date: 3-year follow up in 1989; 5-year follow up in 1999; and 10-year follow up in 1999 The 5-year report also includes information from studies done in Hong Kong (all surgical) and Korea (all chemotherapy); we excluded these results from analysis because they did not randomize between chemotherapy alone and chemotherapy plus surgery	A

*Further details on the included participants are in Table 02
Allocation concealment: A = adequate, see 'Methods of the review'; PAS: p-amino salicylic acid

Characteristics of excluded studies

Study	Reason for exclusion
Jain 2004	Not randomized
Loembe 1994	Not randomized
MRC 1973a	No surgical group
MRC 1973b	No surgical group
MRC 1974b	All participants had surgery
MRC 1976	No surgical group
MRC 1978a	All participants had surgery
MRC 1982	All participants had surgery
MRC 1985	No surgical group
MRC 1986	All participants had surgery
MRC 1993	No surgical group
MRC 1998	No randomization for conservative or surgical treatment: 2 locations, Korea (all chemotherapy without surgery) and Hong Kong (all chemotherapy plus surgery)
Rajasekaran 1998	No surgical group
Rajeswari 1997b	Not a randomized controlled trial, poor methodological quality, randomization method and concealment are unclear; study reports on 33 participants of whom the first 10 were not randomized but all operated because of participation in another trial (one of the included trials ICMR/MRC 1989); the other 23 patients were allocated to chemotherapy only, 4 were lost to follow up for various reasons; of the 19 included in the analysis 3 were operated for neurological deterioration
Seddon 1976	Description of several MRC studies, not a study itself
Upadhyay 1993	All participants had surgery
Upadhyay 1994a	All participants had surgery
Upadhyay 1994b	All participants had surgery
Upadhyay 1994c	All participants had surgery
Upadhyay 1996	All participants had surgery

Table 01
Detailed search strategies.

Search set	CIDG SR*	CENTRAL	MEDLINE**	EMBASE**	LILACS**
1	tuber-culosis	TUBERCULOSIS SPINAL	TUBERCULOSIS SPINAL	tuberculosis spondylitis	spinal tuberculosis
2	spine	Pott* disease	spinal tuberculosis	TUBERCULOUS SPONDYLITIS	TUBERCULOUS SPONDYLITIS tuberculous spondylitis
3	-	1 or 2	tuberculous spondylitis	spinal tuberculosis	Pott's disease
4	-	-	spinal TB	spinal TB	1 or 2 or 3
5	-	-	Pott's disease	vertebral tuberculosis	-
6	-	-	Pott's paraplegia	Pott's disease	-
7	-	-	1 or 2 or 3 or 4 or 5 or 6	1 or 2 or 3 or 4 or 5 or 6	-
	* Cochrane Infectious Diseases Group Specia-lized Register		**Search terms used in combination with the search strategy for retrieving trials developed by The Cochrane Collaboration (Higgins 2005); upper case: MeSH or EMTREE heading; lower case: free text term		

Table 02

Characteristics of included participants.

Characteristic	MRC 1974a	ICMR/MRC 1989
Number enrolled	130	201
Number available at follow up	3 years: 94 (47 in each arm) 5 years: 80 (45 in surgical arm, and 35 in chemotherapy alone arm) (some data available at 18 months)	3 years: 168 (85 in surgical arm, and 83 in chemotherapy alone arm) 5 years: 164 (82 in each arm) 10 years: 156 (78 in each arm) (some data available at 18 months)
Age	Of the 94 people available for analysis at 3 years: 16 were < 15 years and 78 >= 15 years; age range not given	Of the 168 people available for analysis at 3 years: 63 were < 15 years; 105 >= 15 years; age range not given
Gender	Of the 94 people available for analysis at 3 years 52 were male and 42 female	Not given
Number vertebrae involved	1 or 2 in 70 participants > 2 in 24 participants	1 or 2 in 115 participants > 2 in 53 participants
Location of lesions	Thoracic (39 participants) Thoracolumbar (10 participants) Lumbar (45 participants)	Thoracic or thoracolumbar (84 participants) Lumbar or lumbosacral (84 participants)
Kyphosis angle at entry	27° (40 surgical group participants) 24° (33 chemotherapy group participants) (standard deviation not provided)	Only provided for thoracic or thoracolumbar localization: 29° (mean in the surgical group) 29° (mean in the chemotherapy group) (standard deviation not provided) > 20° in 66 of 84 patients with thoracic or thoracolumbar localizations
Mean total bone loss at start of treatment	0.8 U (treatment group) 0.7 U (control group) (standard deviation not provided)	0.8 U (treatment group) 1.0 U (control group) (standard deviation not provided)
Neurological deficit on entry	12/94 participants 12 had incomplete paraplegia but were able to walk (inclusion criterion for this trial)	11/168 participants 11 had incomplete paraplegia but were able to walk (inclusion criterion for this trial)

Table 03

Methodological quality of included studies.

Trial	Sequence*	Concealment*	Inclusion*
MRC 1974a	Unclear	Adequate	Kyphosis angle and neurology: inadequate at 3 and 5 years follow up
ICMR/MRC 1989	Unclear	Adequate	Kyphosis angle: inadequate at 3, 5, and 10 years follow up Neurology: adequate at 3 and 5 years follow up, and inadequate at 10 years follow up

*Generation of allocation sequence, concealment of allocation, inclusion of all randomized (enrolled) participants in the analysis for primary outcomes; details in the 'Characteristics of included studies'

Table 04

Reasons for changing allocated treatment.

Trial	Intervention	No. participants	Reason for change	Details
MRC 1974a	Chemotherapy plus surgery	2	Additional treatment needed	Received extra chemotherapy for persistent sinus
MRC 1974a	Chemotherapy	3	Additional treatment needed	Received extra chemotherapy for progressive neurological deficit
MRC 1974a	Chemotherapy	2	Randomization broken	Needed decompression operation because of progressive neurological deficit
ICMR/MRC 1989	Chemotherapy plus surgery	1	Additional treatment needed	Bone graft displaced posteriorly and a second operation needed to remove the graft
ICMR/MRC 1989	Chemotherapy plus surgery	1	Additional treatment needed	Developed myelopathy with complete paralysis immediately postoperative for which additional chemotherapy was added in third month
ICMR/MRC 1989	Chemotherapy plus surgery	1	Additional treatment needed	Developed a sinus and graft infection that needed a second operation to remove graft
ICMR/MRC 1989	Chemotherapy plus surgery	2	Randomization broken	Problem with exposure of lesion during operation, which had to be abandoned; both received chemotherapy as allocated
ICMR/MRC 1989	Chemotherapy	3	Randomization broken	Needed decompression operation because of progressive neurological deficit
ICMR/MRC 1989	Chemotherapy	2	Randomization broken	Developed abscesses that were treated with additional chemotherapy

Table 05

Mean kyphosis angle (degrees).

	MRC 1974a	MRC 1974a	ICMR/MRC 1989	ICMR/MRC 1989
	Chemotherapy plus surgery	Chemotherapy alone	Chemotherapy plus surgery	Chemotherapy alone
Lesions	T1 to S1	T1 to S1	T1 to L2	T1 to L2
Angle at start	27°	24°	29°	29°
Angle at 18 months	40°	30°	41°	41°
Angle at 3 years	40°	32°	41°	42°
Angle at 5 years	39°	30°	37°	40°
Angle at 10 years	-	-	41°	47°
Increase in angle at 18 months	13° (40 participants)	6° (33 participants)	12° (34 participants)	12° (42 participants)
Increase in angle at 3 years	13° (40 participants)	8° (33 participants)	12° (34 participants)	13° (42 participants)
Increase in angle at 5 years	12° (34 participants)	6° (24 participants)	8° (34 participants)	11° (45 participants)
Increase in angle at 10 years	-	-	12° (28 participants)	18° (41 participants)

Table 06

Deaths from any cause.

Trial	Time of death	Cause of death	Chemo. plus surgery	Chemothe-rapy alone	Group not provided
MRC 1974a	3 months	Unknown, 60 years, 5 weeks after decompression surgery for progressive neurological deficit (change of allocated treatment)	-	1	-
	3 months	Cerebral haemorrhage	1	-	-
	9 months	Pneumonia and dysentery	1	-	-
	11 months	Undiagnosed acute illness	-	1	-
	23 months	Heart failure in 24 year old	-	1	-
	31 months	Sudden death from unknown cause, 53 years	-	1	-
	3 to 5 years	Stomach cancer	1	-	-
	3 to 5 years	Unknown	-	1	-
	3 to 5 years	Heart failure	-	1	-
ICMR/ MRC 1989	1 month	Died < 24 h from disseminated coagulation disorder, woman 25 years	1	-	-
	1 month	Died < 24 h from acute dilatation of the stomach, man 60 years	1	-	-
	1 month	Died from secondary haemorrhage four weeks postoperatively, woman 18 years	1	-	-
	5 months	Died in the 5th month of dyspnoea supposedly from a pulmonary embolism, woman 35 years	-	-	-
	< 1 year	Myocardial infarction	-	-	1
	< 1 year	Burn wounds	-	-	1
	< 1 year	Malignant disease	-	-	1
	< 1 year	Fall from height	-	-	1
	1 to 2 years	Encephalitis	-	-	1
	1 to 2 years	Unknown	-	-	1
	2 to 3 years	Viral infection	-	-	1
	2 to 3 years	Pyrexia of unknown origin	-	-	1
	3 to 5 years	Unknown, nontuberculous	-	-	5
	5 to 10 years	Unknown, nontuberculous	2	2	-

Table 07

Bone loss (U).

Trial	Intervention	Fraction loss: start	Deterioration: 5 yr	Deterioration: 5 yr	Deterioration: 5 yr	Total bone loss: 5yr
MRC 1974a	Chemotherapy plus surgery	0.8	0.2	0.3	0.2	1.0
	Chemotherapy	0.7	0.1	0.1	0.0	0.7
ICMR/ MRC 1989	Chemotherapy plus surgery	0.8	0.3	0.3	0.3	1.1
	Chemotherapy	0.95	0.4	0.5	0.5	1.45

Table 08

Adverse events.

Adverse event	Trial	Chemo. plus surgery	Chemotherapy alone
Operated on the wrong level (excision of healthy bone instead of diseased bone)	ICMR/MRC 1989	1	0
Cases of hepatitis	"	17	11
Graft failure by breakage or displacement, in all these patients the graft spanned more than 3 disc spaces (at 10 year follow up)	"	7	0

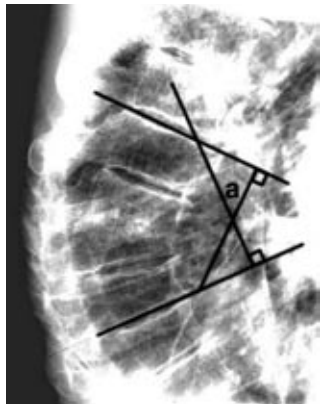


Figure 01
Lateral radiograph of the spine shows a kyphosis angle because two vertebral bodies were destroyed by tuberculosis; the bodies have fused, and further deterioration of the angle is unlikely. The angle is measured by drawing lines parallel to the healthy vertebral bodies above and below the fused bodies.

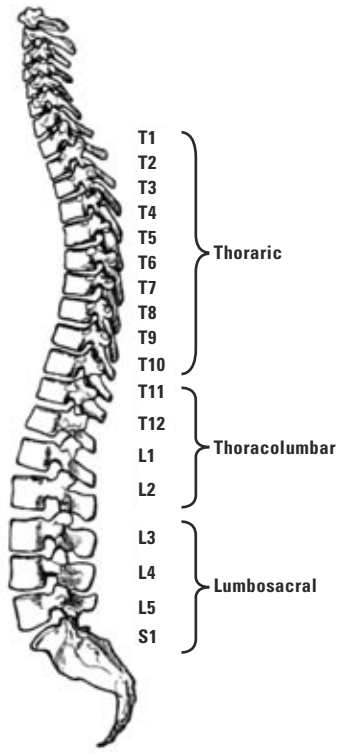


Figure 02
Lateral drawing of the spine illustrating the various levels

Figure 03
Participant flow in MRC 1974a

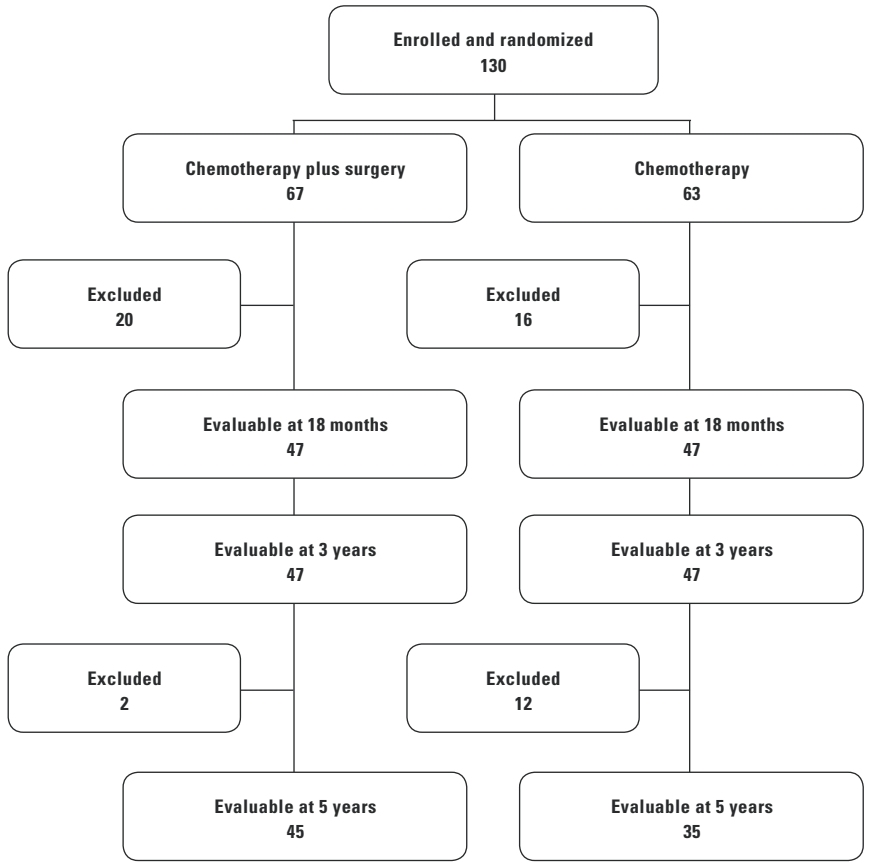
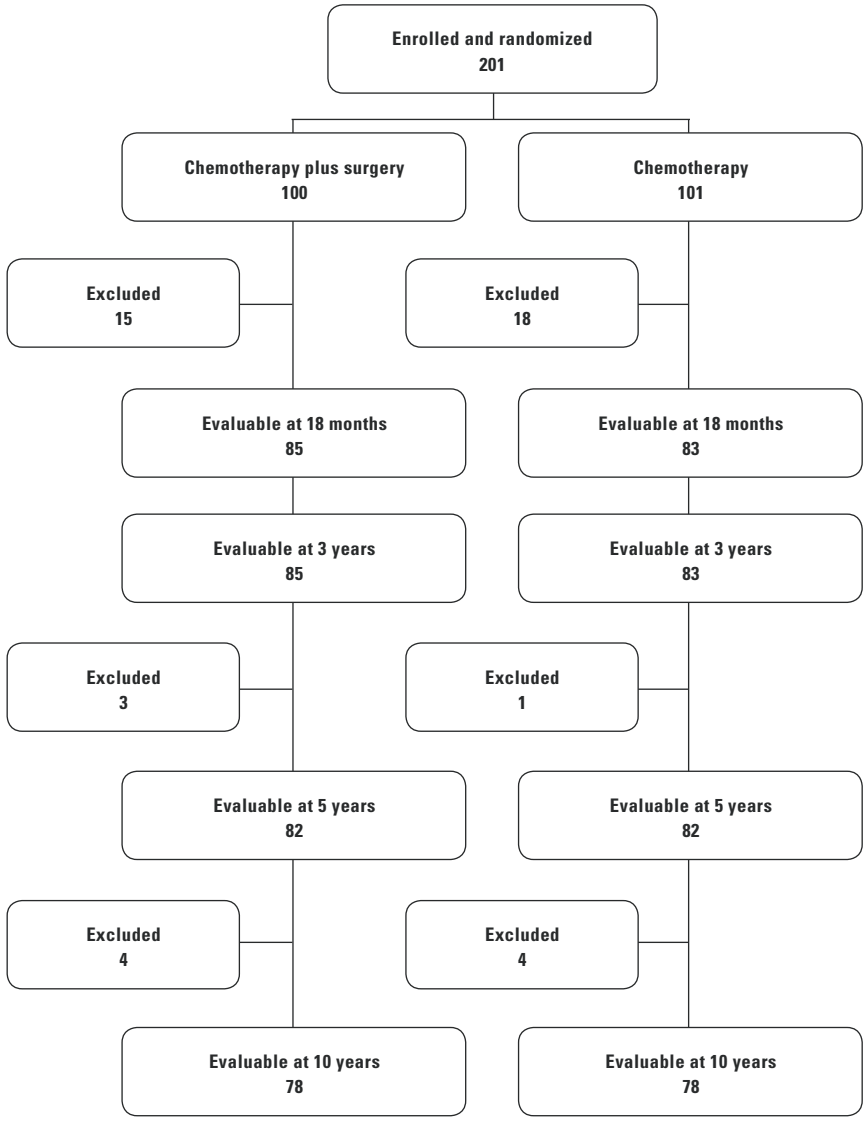


Figure 04
Participant flow in ICMR/MRC 1989

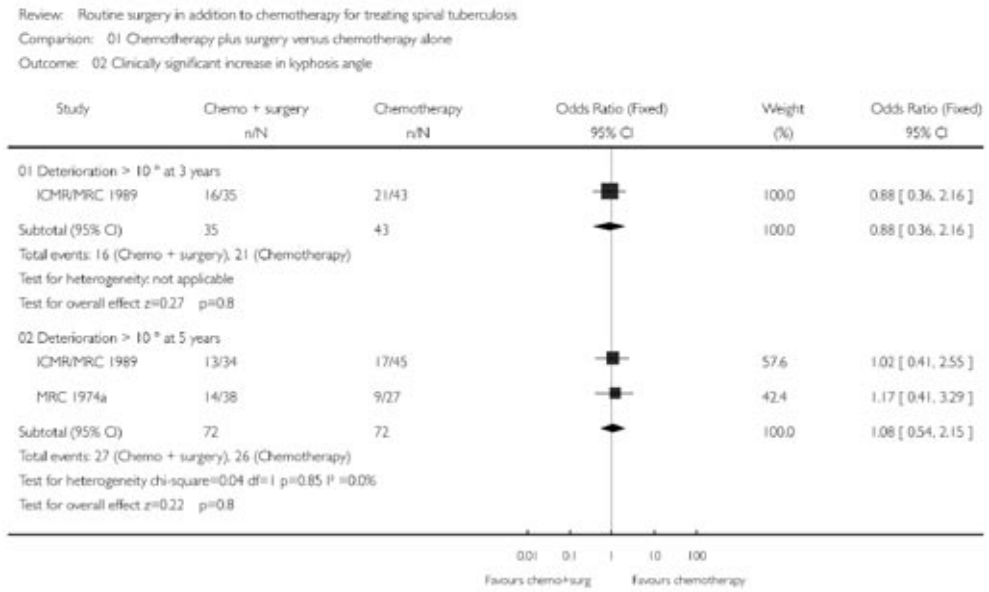


Comparison 01-01 Change of allocated treatment

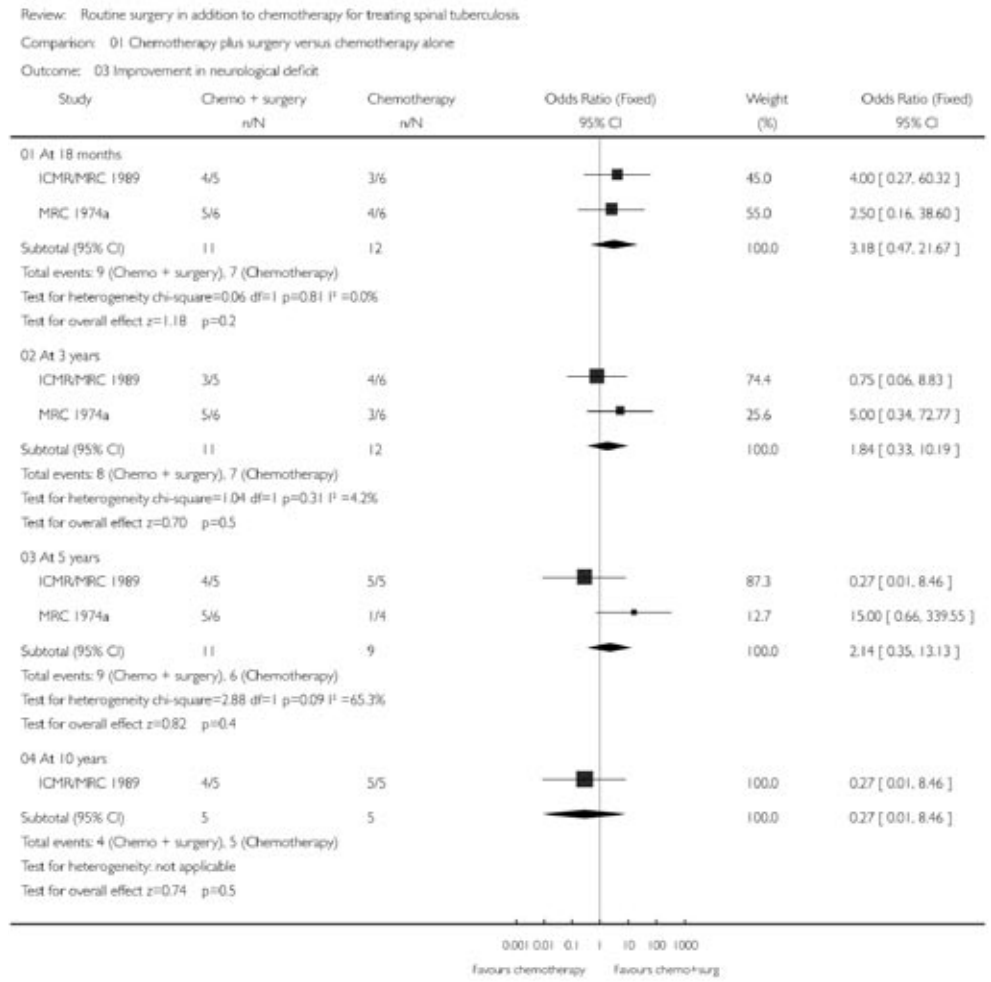
Review: Routine surgery in addition to chemotherapy for treating spinal tuberculosis
Comparison: 01 Chemotherapy plus surgery versus chemotherapy alone
Outcome: 01 Change of allocated treatment

Study	Chemo + surgery n/N	Chemotherapy n/N	Odds Ratio (Fixed) 95% CI	Weight (%)	Odds Ratio (Fixed) 95% CI
01 At 18 months					
ICMR/MRC 1989	5/85	5/83		55.4	0.98 [0.27, 3.50]
MRC 1974a	2/47	4/47		44.6	0.48 [0.08, 2.74]
Subtotal (95% CI)	132	130		100.0	0.75 [0.27, 2.09]
Total events: 7 (Chemo + surgery), 9 (Chemotherapy)					
Test for heterogeneity chi-square=0.42 df=1 p=0.52 I² =0.0%					
Test for overall effect z=0.55 p=0.6					
02 At 3 years					
ICMR/MRC 1989	5/85	5/83		49.9	0.98 [0.27, 3.50]
MRC 1974a	2/47	5/47		50.1	0.37 [0.07, 2.03]
Subtotal (95% CI)	132	130		100.0	0.67 [0.25, 1.82]
Total events: 7 (Chemo + surgery), 10 (Chemotherapy)					
Test for heterogeneity chi-square=0.79 df=1 p=0.37 I² =0.0%					
Test for overall effect z=0.78 p=0.4					
03 At 5 years					
ICMR/MRC 1989	5/82	5/82		52.2	1.00 [0.28, 3.59]
MRC 1974a	2/45	4/35		47.8	0.36 [0.06, 2.09]
Subtotal (95% CI)	127	117		100.0	0.69 [0.25, 1.92]
Total events: 7 (Chemo + surgery), 9 (Chemotherapy)					
Test for heterogeneity chi-square=0.85 df=1 p=0.36 I² =0.0%					
Test for overall effect z=0.70 p=0.5					
04 At 10 years					
ICMR/MRC 1989	5/78	5/78		100.0	1.00 [0.28, 3.60]
Subtotal (95% CI)	78	78		100.0	1.00 [0.28, 3.60]
Total events: 5 (Chemo + surgery), 5 (Chemotherapy)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.00 p=1					

Comparison 01-02 Clinically significant increase in kyphosis angle



Comparison 01-03 Improvement in neurological deficit



Comparison 01-04 Bony fusion

Review: Routine surgery in addition to chemotherapy for treating spinal tuberculosis
Comparison: 01 Chemotherapy plus surgery versus chemotherapy alone
Outcome: 04 Bony fusion

Study	Chemo + surgery n/N	Chemotherapy n/N	Odds Ratio (Fixed) 95% CI	Weight (%)	Odds Ratio (Fixed) 95% CI
01 At 18 months					
ICMR/MRC 1989	39/81	37/82		59.6	1.13 [0.61, 2.09]
MRC 1974a	17/47	20/46		40.4	0.74 [0.32, 1.69]
Subtotal (95% CI)	128	128		100.0	0.97 [0.59, 1.59]
Total events: 56 (Chemo + surgery), 57 (Chemotherapy)					
Test for heterogeneity chi-square=0.65 df=1 p=0.42 I^2 =0.0%					
Test for overall effect z=0.12 p=0.9					
02 At 3 years					
ICMR/MRC 1989	51/81	52/82		57.8	0.98 [0.52, 1.85]
MRC 1974a	24/45	28/39		42.2	0.45 [0.18, 1.12]
Subtotal (95% CI)	126	121		100.0	0.76 [0.45, 1.27]
Total events: 75 (Chemo + surgery), 80 (Chemotherapy)					
Test for heterogeneity chi-square=1.90 df=1 p=0.17 I^2 =47.4%					
Test for overall effect z=1.06 p=0.3					
03 At 5 years					
ICMR/MRC 1989	60/77	60/79		69.3	1.12 [0.53, 2.36]
MRC 1974a	37/45	29/35		30.7	0.96 [0.30, 3.07]
Subtotal (95% CI)	122	114		100.0	1.07 [0.57, 2.00]
Total events: 97 (Chemo + surgery), 89 (Chemotherapy)					
Test for heterogeneity chi-square=0.05 df=1 p=0.83 I^2 =0.0%					
Test for overall effect z=0.21 p=0.8					
04 At 10 years					
ICMR/MRC 1989	64/78	61/78		100.0	1.27 [0.58, 2.81]
Subtotal (95% CI)	78	78		100.0	1.27 [0.58, 2.81]
Total events: 64 (Chemo + surgery), 61 (Chemotherapy)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.60 p=0.5					

Comparison 01-05 Absence of spinal tuberculosis

Review: Routine surgery in addition to chemotherapy for treating spinal tuberculosis
Comparison: 01 Chemotherapy plus surgery versus chemotherapy alone
Outcome: 05 Absence of spinal tuberculosis

Study	Chemo + surgery n/N	Chemotherapy n/N	Odds Ratio (Fixed) 95% CI	Weight (%)	Odds Ratio (Fixed) 95% CI
01 At 18 months					
ICMR/MRC 1989	57/85	53/83		77.8	1.15 [0.61, 2.18]
MRC 1974a	41/47	39/46		22.2	1.23 [0.38, 3.97]
Subtotal (95% CI)	132	129		100.0	1.17 [0.67, 2.05]
Total events: 98 (Chemo + surgery), 92 (Chemotherapy)					
Test for heterogeneity chi-square=0.01 df=1 p=0.93 I^2 =0.0%					
Test for overall effect z=0.55 p=0.6					
02 At 3 years					
ICMR/MRC 1989	77/85	77/83		74.7	0.75 [0.25, 2.26]
MRC 1974a	44/47	39/47		25.3	3.01 [0.75, 12.14]
Subtotal (95% CI)	132	130		100.0	1.32 [0.58, 3.02]
Total events: 121 (Chemo + surgery), 116 (Chemotherapy)					
Test for heterogeneity chi-square=2.35 df=1 p=0.13 I^2 =57.4%					
Test for overall effect z=0.66 p=0.5					
03 At 5 years					
ICMR/MRC 1989	72/82	75/82		61.2	0.67 [0.24, 1.86]
MRC 1974a	37/45	29/35		38.8	0.96 [0.30, 3.07]
Subtotal (95% CI)	127	117		100.0	0.78 [0.36, 1.68]
Total events: 109 (Chemo + surgery), 104 (Chemotherapy)					
Test for heterogeneity chi-square=0.20 df=1 p=0.65 I^2 =0.0%					
Test for overall effect z=0.63 p=0.5					
04 At 10 years					
ICMR/MRC 1989	73/78	70/78		100.0	1.67 [0.52, 5.35]
Subtotal (95% CI)	78	78		100.0	1.67 [0.52, 5.35]
Total events: 73 (Chemo + surgery), 70 (Chemotherapy)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.86 p=0.4					

Comparison 01-06 Deaths from any cause

Review: Routine surgery in addition to chemotherapy for treating spinal tuberculosis
Comparison: 01 Chemotherapy plus surgery versus chemotherapy alone
Outcome: 06 Deaths from any cause

Study	Chemo + surgery n/N	Chemotherapy n/N	Odds Ratio (Fixed) 95% CI	Weight (%)	Odds Ratio (Fixed) 95% CI
01 At 18 months					
ICMR/MRC 1989	4/85	0/83		20.0	9.22 [0.49, 174.01]
MRC 1974a	2/47	2/47		80.0	1.00 [0.13, 7.41]
Subtotal (95% CI)	132	130		100.0	2.65 [0.60, 11.64]
Total events: 6 (Chemo + surgery), 2 (Chemotherapy)					
Test for heterogeneity chi-square=1.60 df=1 p=0.21 I^2 =37.5%					
Test for overall effect z=1.29 p=0.2					
02 At 3 years					
ICMR/MRC 1989	2/47	4/47		88.9	0.48 [0.08, 2.74]
MRC 1974a	4/85	0/83		11.1	9.22 [0.49, 174.01]
Subtotal (95% CI)	132	130		100.0	1.45 [0.42, 4.95]
Total events: 6 (Chemo + surgery), 4 (Chemotherapy)					
Test for heterogeneity chi-square=3.07 df=1 p=0.08 I^2 =67.5%					
Test for overall effect z=0.59 p=0.6					

0.001 0.01 0.1 1 10 100 1000
Favours chemo+surg Favours chemotherapy

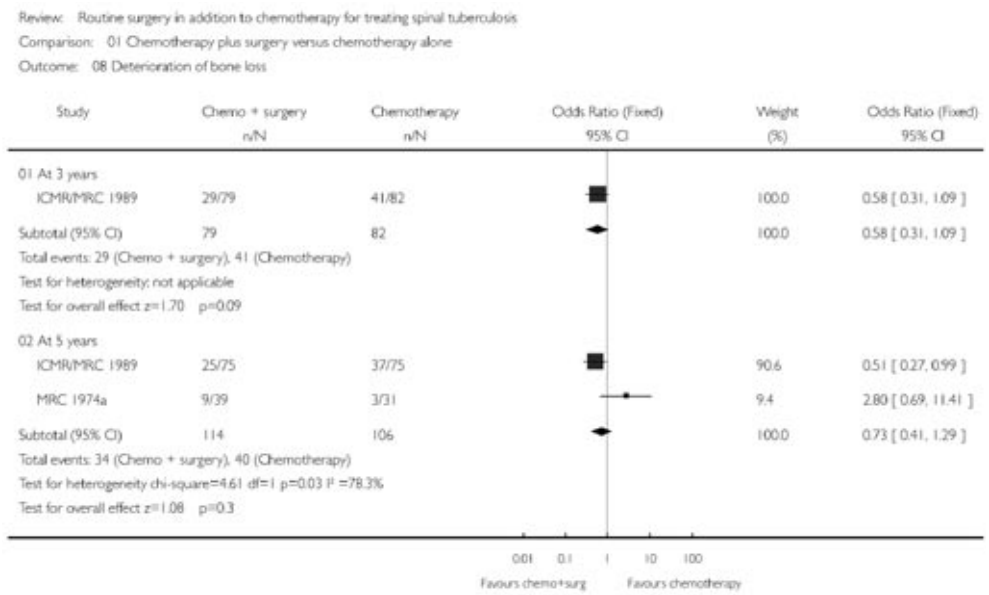
Comparison 01-07 Regained activity level

Review: Routine surgery in addition to chemotherapy for treating spinal tuberculosis
Comparison: 01 Chemotherapy plus surgery versus chemotherapy alone
Outcome: 07 Regained activity level

Study	Chemo + surgery n/N	Chemotherapy n/N	Odds Ratio (Fixed) 95% CI	Weight (%)	Odds Ratio (Fixed) 95% CI
01 At 18 months					
ICMR/MRC 1989	77/85	78/83		66.5	0.62 [0.19, 1.97]
MRC 1974a	43/47	44/47		33.5	0.73 [0.15, 3.47]
Subtotal (95% CI)	132	130		100.0	0.66 [0.26, 1.66]
Total events: 120 (Chemo + surgery), 122 (Chemotherapy)					
Test for heterogeneity chi-square=0.03 df=1 p=0.86 I^2 =0.0%					
Test for overall effect z=0.89 p=0.4					
02 At 3 years					
ICMR/MRC 1989	76/85	78/83		69.1	0.54 [0.17, 1.69]
MRC 1974a	43/47	44/47		30.9	0.73 [0.15, 3.47]
Subtotal (95% CI)	132	130		100.0	0.60 [0.24, 1.50]
Total events: 119 (Chemo + surgery), 122 (Chemotherapy)					
Test for heterogeneity chi-square=0.10 df=1 p=0.76 I^2 =0.0%					
Test for overall effect z=1.09 p=0.3					
03 At 5 years					
ICMR/MRC 1989	74/82	77/82		59.7	0.60 [0.19, 1.92]
MRC 1974a	38/45	29/35		40.3	1.12 [0.34, 3.70]
Subtotal (95% CI)	127	117		100.0	0.81 [0.35, 1.85]
Total events: 112 (Chemo + surgery), 106 (Chemotherapy)					
Test for heterogeneity chi-square=0.54 df=1 p=0.46 I^2 =0.0%					
Test for overall effect z=0.50 p=0.6					
04 At 10 years					
ICMR/MRC 1989	73/78	70/78		100.0	1.67 [0.52, 5.35]
Subtotal (95% CI)	78	78		100.0	1.67 [0.52, 5.35]
Total events: 73 (Chemo + surgery), 70 (Chemotherapy)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.86 p=0.4					

0.01 0.1 1 10 100
Favours chemotherapy Favours chemo+surg

Comparison 01-08 Deterioration of bone loss



CHAPTER 7

PREDICTION OF DEFORMITY IN SPINAL TUBERCULOSIS

Prediction of deformity in spinal tuberculosis
Jutte PC, Wuite S, The B, Van Altena R, Veldhuizen AG
Conditional acceptance for Clin Orthop Relat Res

ABSTRACT

Tuberculosis (TB) of the spine may cause kyphosis. Persisting large kyphosis may cause late paraplegia, ventilatory compromise and cosmetic problems. Routine surgery is not indicated, however large or progressive angles are considered indications for surgical correction. We retrospectively analyzed radiographic and clinical parameters as predictors for the final kyphotic angle in spinal tuberculosis to identify patients at risk of non-favorable outcome (progression > 10 degrees and/or a final angle > 40 degrees) at an early stage of the disease; surgery may be indicated here. Included were 53 patients with active spinal TB located in the thoracic (T1 to T10) and thoracolumbar spine (T11 to L2), with initial angles < 40 degrees. Clinical and radiological data were obtained and analyzed. Univariate analysis revealed no statistically significant independent predictors. Multivariate analysis showed that bone loss > 0.3 (fraction, 1.0 is equivalent to a whole body) on the initial radiograph in combination with a thoracolumbar localization indicated a 38% chance of non-favorable outcome, versus only 3% when bone loss was ≤ 0.3 in combination with a thoracic localization. A simple and clinically useful algorithm for prediction of kyphosis in spinal TB is presented.

INTRODUCTION

Tuberculosis (TB) of the spine demineralizes and destroys the vertebral body, causing pain and deformity (kyphosis); even spinal cord compression can occur (Pott's paraplegia). A persisting large kyphosis may cause several problems. Late paraplegia may develop as a result of myelopathy due to chronically irritated and malnourished spinal cord at the punctum maximum of the curve[15,18,27]. An operation for late paraplegia is very difficult and prone to major complications without subsidence of the neurological deficit[19]. Another problem with large kyphosis can be ventilatory compromise because of diminished intrathoracic volume[29]. Furthermore, many patients have problems with the cosmetic aspects of a large hunchback[14].

The British Medical Research Council Working Party on Tuberculosis of the

Spine (MRC) performed a series of trials to investigate the various methods of treatment of spinal TB. They concluded that chemotherapy on an outpatient basis is sufficient to treat the majority of people and routine surgery is not beneficial[2-12]. This conclusion is attractive since most patients live in countries with limited resources. However, patients who had an initial kyphosis angle > 30 degrees developed mean final angles between 50 and 73 degrees after 10 years[23]. Many authors state that kyphosis > 30 degrees is likely to deteriorate. Large or progressive angles are considered indications for surgery[1,13,16,18-21,23,27,28,33-36]. With modern instrumentation techniques, large kyphotic angles can be corrected and correction can be maintained over the years[13,19-22,28,30,34,35].

Prediction at an early stage of patients at risk of developing large and/or progressive kyphotic angles can guide clinical decision making. Rajasekaran and Shanmugasundaram developed a formula to predict the final kyphotic angle[25]. Unfortunately they included also patients with severe kyphosis who had a clear indication for surgery. Moreover, the reported accuracy of this formula varies widely (34% to 90%)[23,25]. Therefore, a clear guideline for clinical decision making still lacks.

The aims of this study were to assess which radiographic and clinical parameters are early predictors for the final kyphotic angle in spinal tuberculosis. Our ultimate goal was to develop a means of identification of patients at risk of severe or progressive kyphosis at an early stage of the disease.

PATIENT AND METHODS

A retrospective radiographic survey on patients with active spinal TB in the normal range of kyphosis (T1 to L2) was performed. The radiographs and clinical data were obtained from the Beatrixoord Tuberculosis Center of the University Medical Center Groningen in the Netherlands.

Inclusion criteria were patients with active spinal TB. A lesion is active when there is loss of the thin cortical outline and when there is rarefaction of the affected vertebral bodies. Inactive disease is considered bony fusion of the affected vertebral bodies or sclerosis of the contiguous surface of the affected vertebrae with reduction or disappearance of the intervening disc space[2]. Localization of the lesions had to be in the thoracic (T1 to T10) or thoracolumbar spine (T11 to L2). Furthermore, a minimum follow-up of six months was required, this being the standard treatment period for chemotherapy[17]. Radiographs at entry and final follow-up had to be of sufficient quality. Only patients older than 15 years of age were included to eliminate possible bias by growth. Patients with initial angles < 40 degrees were considered for this study.

Medical files, microfilms and a computerized archive were used to extract clinical data on age, sex, duration of symptoms, neurology and medication. Radiographs at entry and final follow-up were measured. The bone loss was measured on the initial lateral radiograph using the differences in anterior and posterior height in comparison with adjacent unaffected vertebrae (Figure 1). A negative bone loss means that the total measured surface of the affected vertebra is higher than the mean indexed surface. The initial and final angles were measured on the lateral and AP radiographs (Figure 2). Interobserver reliability of the measurement method for bone loss and deformity angle was assessed by having a randomly selected series of 10 radiographs measured by three independent observers (PJ, SW, BT). They were blinded for the measurement values of the other observers.

STATISTICAL ANALYSIS

Comparisons were made between people with a favorable outcome and a non-favorable outcome. A favorable outcome was defined as neither having a final kyphosis of 40 degrees or more, nor having progressed 10 degrees or more from the initially measured angle. An unfavorable outcome was a final kyphosis ≥ 40 degrees or ≥10 degrees of progression. For continuous variables, univariate analysis was performed using the Student t-test for independent samples. The Pearson Chi-square test was used for categorical variables when all cells of the contingency table contained at least five patients. Otherwise the Fisher exact test was used. An intraclass correlation coefficient was used to measure interobserver reliability of the measurement method for bone loss and deformity angle.

A multivariate logistic regression with stepwise backward selection was used to identify predictors. Elimination was continued until no variables with a p-value > 0.25 were left. A predefined maximum of two variables in the final multivariate model was considered appropriate to prevent over fitting. A receiver operating characteristic (ROC) curve was used to assess diagnostic performance of the final model. The ROC curve is constructed by plotting the sensitivity on the y-axis and the false-positive rate (1 – specificity) on the x-axis. The larger the area under the curve, the larger the predictive performance of the model. A prediction rule with perfect diagnostic performance would have an area under the ROC curve of 1.0. Flipping coins would have an area under the curve of 0.5. The final regression model was used to construct an easy-to-use algorithm for use in clinical practice. All statistical procedures were performed using the software package SPSS version 12.0 (SPSS, Chicago).

RESULTS

Fifty-three patients fulfilled the inclusion criteria, 30 men and 23 women (57% and 43%). The patients had a mean age of 46 years with a mean follow-up of 54 months (Table 1). All patients used Isoniazid and 57% of the patients used Pyrazinamide (Table 2).

Figure 1
Expected normal vertebral height is calculated by measuring the anterior and posterior vertebral height of the first normal vertebra cranially and caudally from the affected lesion divided by four. The mean height of each affected vertebra is calculated by adding up the anterior and posterior height of the affected vertebra and dividing by two. Bone loss per affected vertebra is then calculated as follows: 1 – (mean height affected vertebra / mean height normal vertebrae). Adding up the bone loss per vertebra will give the total bone loss.

$$\text{Bone loss A} = 1 - \left(\frac{\frac{0+5}{2}}{\frac{10+10+10+10}{4}} \right)$$

$$\text{Bone loss B} = 1 - \left(\frac{\frac{5+5}{2}}{\frac{10+10+10+10}{4}} \right)$$

Total = 0.75(A) + 0.50(B) = 1.25

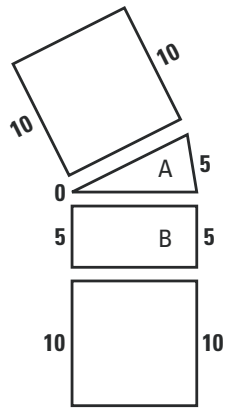
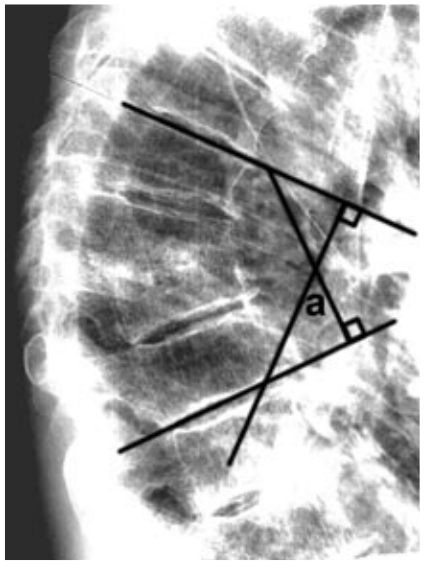


Figure 2
Measurement of the kyphotic angle is done with the method according to Cobb: a straight line is drawn through the superior surface of the first normal vertebra cranially from the lesion, and a second line through the inferior surface of the first normal vertebra caudally from the lesion. These two lines will cross and form angle A[2]. In mild angles perpendiculars can be drawn, and angle A is measured at their intersection.



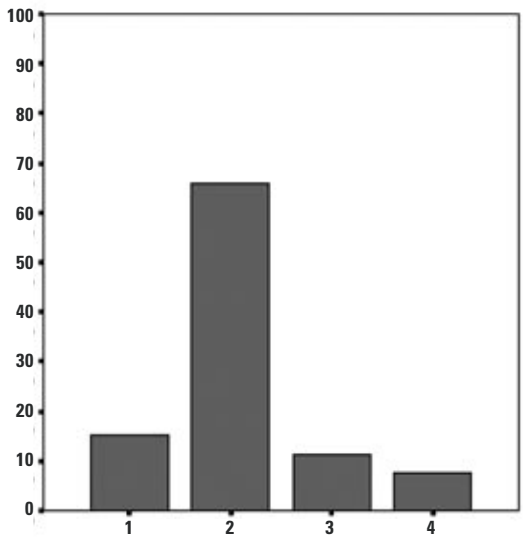
Back pain was present in 77% of the patients, and 15% had neurological deficit. The average number of affected vertebrae was 2.1. In 81% of the cases, one or two vertebrae were affected; in 19% three or four (Figure 3). The lesions were located in the thoracic region in 21 patients (40%) and in the thoracolumbar in 32 patients (60%). T11 was most commonly affected (34% of cases) (Figure 4).

An unfavorable outcome was found in eleven patients (21%). In 10 patients (19%) a progression of more than 10 degrees was found . In four patients (8%) a final angle of more than 40 degrees was found. Three of them had a progression of more than 10 degrees as well.

The most powerful predictors for a favorable or non-favorable outcome were bone loss and localization. Univariate analysis indicated that indexed initial bone loss more than 0.3 (OR 8.7, p = 0.07) and thoracolumbar involvement (OR 2.6, p = 0.2) were the most important predictive variables (Table 3). Multivariate analysis showed that the combination of bone loss and localization should be used in the predictive model. The intraclass correlation coefficient of the measurement method to determine bone loss was 0.97.

A 97% chance of a favorable outcome was found when the patient had neither bone loss > 0.3 nor a thoracolumbar localization of the lesion, while a 62% chance of a favorable outcome was found if both of these variables were present. The area under the ROC curve of this predictive model was 0.74 (Figure 5). A clinically useful algorithm was developed using the four possible combinations of the two variables (Table 4).

Figure 3
Percentage of patients with number of affected vertebrae.



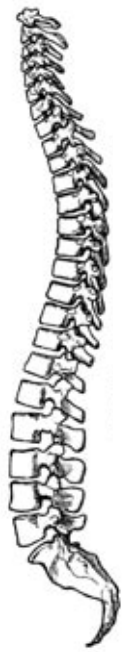


Figure 4
Localization and total number of affected vertebrae for all cases.

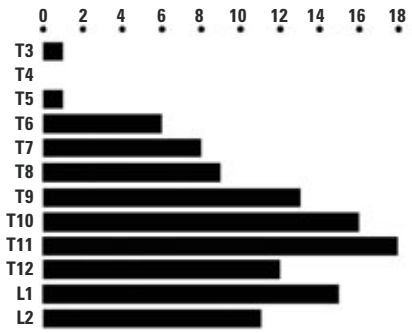
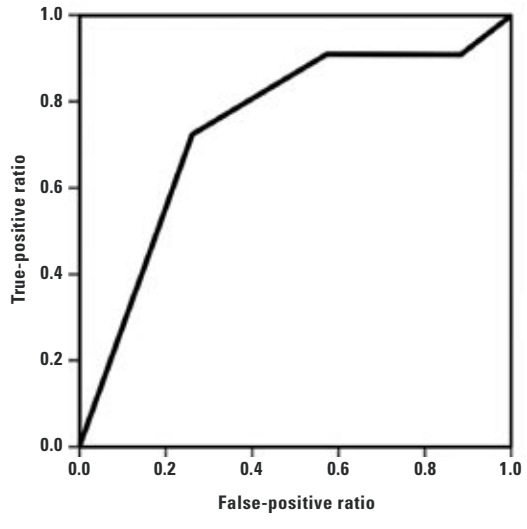


Figure 5
The receiver operating characteristic (ROC) curve has an area under the curve of 0.74, indicating adequate predictive performance of the final model.



DISCUSSION

To identify patients at risk of developing severe or progressive kyphosis at an early stage of spinal tuberculosis, an analysis of radiographic and clinical parameters as predictors for the final kyphotic angle was performed. In the absence of bone loss > 0.3 and without thoracolumbar localization the chance of a favorable outcome was 97%, while this was 62% when both of these parameters were present. The area under the ROC curve of this final model was 0.74, indicating an adequate predictive performance.

Patients with initial kyphosis angles > 40 degrees were excluded because deterioration is very likely in this group given the results from the MRC studies[23]. Prediction of the final angle is of minor importance for these more severe cases because they are generally indicated for surgical correction at the time of diagnosis. Many authors even consider a kyphotic angle > 30 degrees or a progressive angle an absolute indication for surgery[1,13,16,19-23,27,28,30,34-36]. We included the patients with a kyphotic angle between 30 and 40 degrees to find out whether this 30-degree limit could be justified with our data. In the group of patients that had initial angles between 30 and 40 degrees there were only 2 of 15 patients that had a non-favorable outcome, compared to 9 of 38 patients that had initial angles < 30 degrees. This suggests that in the absence of pain or neurological deficit there is no need to routinely operate patients with initial kyphosis angles < 40 degrees.

We excluded lumbar lesions from our analysis because physiological lordosis in the lumbar region (L3-L5) interferes with accurate measurement of the gibbous deformity. The large bodies and the vertical articular facets of the lumbar spine allow the collapse to occur more by telescoping than by angulation. The lumbar kyphosis is usually minimal, and expressed as foreshortening of the trunk rather than kyphosis[24-26,32].

A limitation of our study is the large time span in the course of which patients were treated and the different chemotherapy regimens. More specifically, after the introduction of Pyrazinamide relapse rates for pulmonary tuberculosis dropped from 7.8% and 20.3% after two and five years follow-up to 1.4% and 3.4%, respectively[10]. There was no influence of Pyrazinamide on the outcome in our patients. There are no previous reports in the literature about the influence of Pyrazinamide on spinal TB. Other clinical parameters like age, sex and duration of symptoms did not show any predictive value either.

The thoracolumbar area might be more at risk of kyphosis because the rib cage provides no structural support here, which is in concordance with the finding that deformities in cases of thoracolumbar localization of the lesions are larger[36]. It has been stated that the number of affected vertebrae is a determinant of the kyphotic angle: more vertebrae lead to larger kyphotic angles[31]. This was not the case in our analysis. Nineteen percent of our patients had three or four affected vertebrae, and there was no relation with unfavorable outcome.

Rajasakaran and Shanmugasundaram constructed a formula to predict the final kyphotic angle according to the initial amount of bone loss, independently of lesion localization or initial kyphotic angle[25]. A 90% accuracy of prediction was reported. However, a cross-validation of the formula revealed that only in 34% of the cases the correct angle was predicted with a margin of error of 10 degrees. It was concluded that the angle of kyphosis at 10 years cannot be accurately predicted based on the initial vertebral loss in most patients[23]. Applying the original formula on our data it was possible to predict the final angle within 10 degrees in 64% of our cases. However, the prediction of unfavorable outcome is in our opinion of more value than the prediction of the final angle, considering the margin of error here. We feel that 10 degrees is too wide a margin to guide clinical decision making.

Our ultimate goal was to predict which patients were at risk of an unfavorable outcome, but it turned out that we were better in predicting favorable outcome. Our algorithm is simple and can be used in clinical practice to identify at an early stage of spinal TB those patients at risk of unfavorable outcome as well as patients that will very likely have a favorable outcome. We recommend its use to guide clinical decision-making. Treatment can be started conservatively for all patients with kyphosis angles < 40 degrees, but one should monitor extra carefully those patients with initial bone loss >0.3 in combination with a thoracolumbar localization.

TABLES

Table 1
Descriptive patient characteristics.

Variable	Mean	Range
Age (years)	46	18 to 83
Follow-up (months)	54	6 to 238
Duration of symptoms (months)	13	0 to 192
Indexed total bone loss T1-L2	0.5	-0.18 to 1.62
Indexed total bone loss T1-10	0.65	0.11 to 1.62
Indexed total bone loss T11-L2	0.47	-0.18 to 1.46
Initial kyphotic angle	20	-22 to 38
Initial anteroposterior deformity angle	4	0 to 16
Final kyphotic angle	23	-28 to 55

Table 2
Use of modern drugs in percentages for all patients.

Drug regiment	ISO	RIF	PYR	ETH
Percentage of patients	100	47	57	34

ISO=Isoniazid, RIF=Rifampicin, PYR=Pyrazinamide, ETH=Ethambutol

Table 3
Univariate analysis of favorable versus non-favorable group.

Group	Favorable (42)	Non-favorable (11)	P-value
Mean age	49	45	0.6
Mean initial kyphotic angle	23	20	0.4
Mean initial AP angle	5	3	0.5
Female gender	19 (45%)	4 (36%)	0.7
≥ 3 affected vertebrae	8 (19%)	2 (18%)	1.0
Pyrazinamide use	22 (52%)	8 (73%)	0.3
Thoracolumbar involvement	24 (57%)	8 (73%)	0.5
Bone loss > 0.3	24 (57%)	10 (91%)	0.07
Initial angle 30-40 degrees	13 (31%)	2 (18%)	0.5

Table 4
Probability of favorable outcome for all combinations of the two strongest predictors.

>0.3 bone loss	thoracolumbar involvement	probability of favorable outcome
Yes	Yes	62%
Yes	No	81%
No	Yes	93%
No	No	97%

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CHAPTER 8
INTERPRETATION AND IMPLICATIONS

An increasing number of patients with bone and joint tuberculosis (BJTB), including spinal tuberculosis (TB), has been seen in the Netherlands in recent years, raising our orthopaedic interest in TB. In Chapter 2 an analysis was made of this increased incidence. All data were extracted from the Netherlands Tuberculosis Register (NTR) held by the Royal Netherlands Tuberculosis Association KNCV. This unique register contains data on over 95% of all TB patients in the Netherlands from 1993. Between 1993 and 2000, a total of 532 patients with BJTB were registered, 308 (58%) with spinal lesions. This is in accordance with the percentages in the literature.

There was no significant change in the incidence of BJTB in the native Dutch population during the study period. Univariate analysis showed that the increase in incidence was restricted to foreign nationals from endemic areas. They constituted a relatively larger proportion of people with BJTB and spinal TB. The fact that certain ethnic groups showed a significantly higher chance of developing BJTB surprised us. This means that, with the same infection prevalence, some ethnic groups progress more often to BJTB, suggesting a genetic component in TB expression. A detailed genetic analysis might shed new light on this issue. Regarding the genetics of the micro-organism, DNA type clustering of the different strains of *M. tuberculosis* did not reveal any association between certain strains and BJTB.

The study demonstrated that only 15% of BJTB patients also suffered from pulmonary TB. The routinely taken chest radiograph hardly contributes in differential diagnostics and may never be used to exclude the possibility of spinal TB in differential diagnostics. We cannot compare the Dutch situation to neighbouring countries, as there are no recent reports on this topic in the literature.

The epidemiological analysis revealed a 3-month doctors' delay in diagnosis for spinal TB. This clearly demonstrates that many physicians in the Netherlands have a problem diagnosing spinal TB. The potentially devastating consequences of misdiagnosis are illustrated in Chapter 3. Two patients are reported who were misdiagnosed as having malignant lesions of the spine instead of TB. Both received radiotherapy, both experienced growth of the lesion, and in one patient the neurological deficit increased and did not reverse after initiation of the proper TB treatment.

The most common diagnosis in patients with spinal lesions of unknown origin is obviously metastasis. To prove the metastatic origin of a lesion screening is done for primary lesions like carcinoma of the prostate, lung or breast. If the primary lesion is revealed, radiation therapy is started. If not, biopsy is mandatory to confirm malignancy and exclude TB before radiation therapy is started. Radiation

is an aggressive and potentially harmful therapy that locally aggravates TB, as was demonstrated by our cases. The local immune response is indispensable in conquering the lesion; radiation severely affects this local response.

The diagnostic pathway should start with a thorough anamnesis and past medical history, which is simple and very helpful in diagnosing TB. The risk of developing tuberculosis increases manifold if a patient belongs to a risk group like immigrants from endemic countries, people with previous TB or people using immunosuppressive medication. Work-up often comprises a Mantoux test. Whether a positive test is helpful in diagnosis if patients are immigrants from endemic countries or born in a period when TB was very common is questionable; a positive Mantoux test may be proof of active disease as well as of previous exposure. Laboratory tests are not specific either. Radiographs and especially MRI are very helpful in diagnosing spinal TB. Typically, affected vertebral bodies on both sides of a destroyed disc are found; vertebral collapse and abscess formation can be seen too. However, the only definite proof of TB is a positive culture of material from the lesion. Because even a negative culture does not exclude TB and cultures may take up to 10 weeks before the results are known, histology is often mandatory. A newer means of proving TB is a molecular diagnostic technique called polymerase chain reaction (PCR). It is a nucleic acid amplification technique that shortens the time required to detect and identify *M. tuberculosis*. This technique does not replace the need for routine acid fast bacilli smear or culture, but it can greatly improve confidence in the clinical diagnosis pending culture results. If trochar biopsy fails to deliver a sufficient amount of material for examination, surgery is indicated. Surgery can provide sufficient biopsy material for histology and cultures, as well as instant decompression of the spinal cord.

The main reasons for the lengthy delay in diagnosis and misdiagnosis of spinal TB are low incidence, low index of suspicion, declined expertise and accepted failed biopsy. It is difficult to educate the patients about spinal TB, but we can at least try to promote awareness among our colleagues. Perhaps a nationwide panel of experts should be formed to advise about difficult cases. Spinal TB patients should be referred to centres of excellence where multidisciplinary care can be provided.

The length of treatment for spinal TB is commonly longer than the standard short-course 6-months used for other forms of TB. Clinical practice in the Netherlands is chemotherapy from six to more than 13 months. There is no uniform advise regarding length of treatment for spinal TB in the literature. Since compliance is important to prevent the emergence of resistant strains of *M. tuberculosis*, length of treatment should be no longer than strictly necessary. To assess whether the short-course 6-month treatment is as good as longer treatment regimens (> 6 months), we performed a review of the English, German, and French literature in Chapter 4. Outcome was evaluated in terms of relapse rates after successful treatment.

No randomised controlled trials were identified. Reasons for choosing the length of treatment were not stated. There were four publications with the short-course 6-month treatment regimen with a total of 82 adult patients. All the patients had undergone surgical intervention. After treatment completion, all the patients were declared cured. The relapse rate was 0%. There were 10 publications with a > 6-month treatment regimen, with a total of 274 patients. A proportion of the patients had undergone surgical intervention (162/274). Before completing treatment eight of 245 patients died, seven from unrelated causes and one from TB. A total of 93% were cured (227/245). Relapse occurred in 2% (4/218).

No differences were identified between 6 and >6 months regimens. There were no differences between the several regions of the world in characteristics of participants or outcome. The relapse rates were comparable. The fact that surgery was performed may have contributed to the low rate of relapse, although other studies done before the introduction of Pyrazinamide (1978), showed no statistically significant differences between operated and non-operated groups on relapse in spinal TB treatment.

Regarding the role of surgery, it seems logical that debridement or resection of the diseased tissue speeds up recovery. It diminishes the bacterial load the medication has to take care of, and the medication is delivered better because the necrosis, with its absence of vascularity, is gone. At present, we are planning a trial to evaluate local TB activity with positron emission tomography (PET). This will hopefully enable us to critically and precisely follow the result of treatment and it may even show that the length of chemotherapy treatment can be reduced further. The role of surgery in this aspect can be assessed too. This can typically be the kind of research that a high-tech country like the Netherlands can perform to contribute to the general knowledge of TB treatment.

Another means of shortening treatment duration may be the development of new medication. The last major drug introduced was Pyrazinamide, more than 25 years ago. Apparently TB is not an interesting disease for the pharmaceutical companies. This is the consequence of our economically-driven system: when there is little money to earn, stockholders cannot be satisfied and research agendas are set in other, more lucrative, directions. Of course, TB is mainly a disease of the poorer parts of the world, but patient numbers are still increasing and 2,000,000 people die annually from TB! It is crystal-clear that new medication is needed desperately.

One of the problems in spinal TB is the development of psoas abscesses that can become very large. It is questionable whether chemotherapy reaches sufficiently high concentrations inside fluid collections like psoas abscesses and pleural fluid. The intralesional concentrations of Isoniazid (ISO), Rifampicin (RIF) and Pyrazinamide (PYR) are not known. Insight into drug penetration is important since

sub-therapeutic drug concentrations may result in selection of a resistant bacterial population and lead to treatment failure. We performed a study (Chapter 5) on the concentrations of ISO, RIF and PYR inside psoas abscesses and tuberculous pleural effusions to gain insight into the actual intralesional concentrations in order to verify the possibility of sterilising lesions by chemotherapy alone. Concentrations in serum, pleural effusion (6 patients) and psoas abscess fluid (10 patients) were determined. They were below minimal inhibitory concentration (MIC) values in none of 15 patients for ISO, in 2 of 13 for RIF, and in 8 of 9 for PYR. The ratio of the maximal concentration (Cmax) to the MIC is a measure for the potency of a drug; a Cmax: MIC-ratio > 4 is indicative of effectiveness. This ratio was always greater than 4 for ISO, in 4 of 13 for RIF, and in none of 9 for PYR. In 5 of 8 patients receiving all three drugs, both RIF and PYR had Cmax:MIC ratios below 4, indicating intralesional sub-therapeutic drug levels. This local monotherapy with ISO carries the risk of selection of resistant bacterial populations and subsequent failure of treatment. Seven percent of TB patients in the Netherlands in 2000 in whom positive cultures were found had resistance to ISO.

We use percutaneous techniques to drain pleural effusions. In psoas abscesses, percutaneous drainage or even surgical debridement is advised to reduce the intralesional bacterial load and shorten the time to resolve the lesions. Diminishing the bacterial load may help reduce the chance of formation of drug resistance. Even the length of medical treatment may be reduced, thereby probably increasing compliance. This will further decrease the chance of formation of resistant strains. Drainage or surgical debridement is strongly advised as additional therapy for patients with pleural effusion or psoas abscesses.

Treatment in general for TB is aimed at completing the course of medication and prevention of relapse. Because of the special problems spinal TB poses, treatment must not only be aimed at local control and prevention of relapse, but also at prevention of deformity, pain and paraplegia. It must be multidisciplinary. Potential benefits of surgery in spinal TB are less kyphosis, a higher percentage of bony fusion, quicker relief of pain, immediate relief of compressed nerve tissue, quicker bony fusion and fewer relapses. The exact benefits of surgery are however not clear and there is ongoing controversy about the role of surgery since the 1960s. Surgeons promote surgery and non-surgeons state that chemotherapy alone is sufficient. The goal of Chapter 6 was to perform a systematic Cochrane review of the literature to compare chemotherapy to chemotherapy plus surgery, to evaluate the best evidence assessing the role of surgery.

Two randomized controlled trials (331 participants) met the inclusion criteria. They were conducted in the 1970s and 1980s with follow-up reports available after 18 months, three years, and five years; one trial also reported 10 years follow up. Completeness of follow up varied at the different time points, with less than 80% of participants available for analysis at several time points. There was no statistically significant difference for any of the outcome measures: kyphosis angle, neurological deficit (none went on to develop this), bony fusion, absence of spinal tuberculosis, death from any cause, activity level regained, change of allocated treatment, or bone loss. Neither trial reported on pain. Of the 130 participants allocated to chemotherapy only, 12 had a neurological deficit and five needed a decompression operation. One trial suggested that an initial kyphosis angle greater than 30° is likely to deteriorate, especially in children.

Data are insufficient to be clear whether chemotherapy plus surgery is better than chemotherapy alone (with surgery used when clinically indicated). The investigated trials were performed some years ago, and current medication and operative techniques are far more advanced. However, these results indicate that routine surgery cannot be recommended unless within the context of a large, well-conducted randomized controlled trial.

Clinicians may judge that surgery may be indicated in subgroups of patients with an initial kyphosis angle greater than 30° (especially in children) or progressive or persistent neurological deficit with spinal cord compression despite chemotherapy but there are no randomized comparisons to support this. Future trials need to assess routine surgery and need to be large enough to assess outcomes properly. They need to assess pain and the patient's view of their disease and treatment. These trials also need to address subgroups of patients with spinal tuberculosis to establish the role of surgery for specific indications.

It would be ideal to identify at an early stage subgroups of patients likely to benefit from surgery. The surgical procedure is much easier to perform at an early stage of the disease, when less deformity has to be corrected. In Chapter 7 we evaluated radiographic and clinical parameters as early predictors for the final kyphotic angle.

Univariate analysis revealed no significant independent predictors. Multivariate analysis showed that indexed bone loss > 0.3 in combination with a thoracolumbar localisation indicated a 38% chance of non-favourable outcome (progression >10 degrees and/or a final angle > 40 degrees) versus only 3% when bone loss was ≤ 0.3 in combination with a thoracic localisation. The area under the receiver operating curve of this final model was 0.74, indicating an adequate predictive performance. A simple and clinically useful algorithm for early prediction of kyphosis in spinal TB was developed which identifies at an early stage of spinal TB those patients at risk of unfavourable outcome as well as patients who will very likely have a favourable outcome.

Our goal was to predict which patients are at risk of an unfavourable outcome, but it turned out that we were better in predicting favourable outcome! We recommend use of the algorithm to guide clinical decision-making.

Treatment can be started conservatively for all patients with kyphotic angles smaller than 40 degrees, but one can monitor extra carefully those patients with initial bone loss >0.3 in combination with a thoracolumbar localisation. Future investigations in larger populations may provide further fine-tuning of the algorithm to optimise individual treatment.

CHAPTER 9
SUMMARY

CHAPTER 1

Introduction and aims of the thesis

Tuberculosis (TB) is an ancient infectious disease caused by the *mycobacterium tuberculosis*. TB has always been present throughout history. The incidence in advanced countries steadily declined untill the beginning of the 1990's when there was a resurgence of TB in the whole world. Approximately two million people die from TB each year worldwide. In the Netherlands there are about 1500 new patients each year. People commonly develop pulmonary TB; in four percent bone and joint tuberculosis (BJTB) develops, of which 50% is located in the spine.

BJTB (including spinal TB) demands a multidisciplinary approach. Chemotherapy is the mainstay of treatment, a standard combination of Isoniazid (ISO), Rifampicin (RIF), and Pyrazinamid (PYR) is given, sometimes a fourth drug is added: Ethambutol (ETH). Spinal TB is a very serious form of TB that demineralises and destroys the spine, sometimes even leading to a hunchback (kyphosis). Furthermore, this destruction may cause compression on the spinal cord and give paraplegia.

The main goal of this thesis is to provide insight into spinal tuberculosis from a Dutch perspective: to establish the size of the problem in the Netherlands, analyse the reasons for misdiagnosis, assess optimal treatment, verify if this is truly optimal, establish the effect of surgery, and find out when surgery is needed.

CHAPTER 2

Increase in bone and joint tuberculosis in The Netherlands

In Chapter 2, an analysis was made of the increase in Bone and Joint Tuberculosis (BJTB) in the Netherlands during recent years. All data were extracted from the Netherlands Tuberculosis Register (NTR) held by the KNCV Tuberculosis Foundation. The increased incidence was seen between 1993 and 2000. A total of 532 cases of BJTB was foundin this period.

In the native Dutch population there were no significant changes in the incidence of BJTB during the study period. Univariate analysis showed that the increase in incidence was restricted to non-Dutch people from endemic areas. They constituted a relatively larger proportion of people with BJTB. Furthermore, a relatively larger percentage developed BJTB, meaning that, with the same infection prevalence, some ethnic groups progress more often to BJTB and/or less often to other forms of TB. Women were relatively more affected (OR 1.57) with BJTB and there was an association with increasing age.

It is important to note that only 15% of BJTB patients in our series also suffered from pulmonary TB. A normal chest radiograph does not rule out BJTB.

In our study a lengthy delay by both patients and doctors was found for BJTB (mean period 32 weeks), probably explained by a low index of suspicion and declining expertise. TB is still prevalent and should be considered in differential diagnosis of unknown lesions in the spine.

CHAPTER 3

Misdiagnosis and mistreatment of spinal tuberculosis

In Chapter 3 a previously undescribed misdiagnosis and subsequent mistreatment with radiation for tuberculosis of the spine in two patients is reported. An analysis of the reasons for misdiagnosis was made.

Two patients were assumed to have malignancies. Both received radiotherapy, both experienced growth of the lesion and only then the diagnosis TB was established. In one of the patients the neurological deficit did not reverse after initiation of the proper TB treatment.

The work-up of patients with spinal lesions of unknown origin should start with their history. The risk of developing tuberculosis increases manifold if a patient belongs to a risk group, as both patients did; one had a history of TB in his hip, the other was an immigrant from an endemic area. Imaging features were overlooked in both: spinal tuberculosis gives affected vertebral bodies on both sides of a more or less destroyed disc, large paraspinous abscesses, a thick rim of contrast enhancement around the paraspinous and intraosseous abscesses, calcifications within the paraspinous collections, and a fragmentary pattern of osseous destruction.

It is not seldom that radiation therapy is provided for suspected malignant spinal lesions without histological confirmation. In all patients with suspected metastasis of unknown origin, screening is done for the most obvious primary lesions: prostate specific antigen, radiographs of breast and chest. If this reveals a primary lesion, radiation therapy is started. If not, biopsy is mandatory. Radiation therapy is an aggressive and potentially harmful therapy, and should only be applied in the presence of a clear histologic diagnosis ruling out tuberculosis. Secondary trochar biopsy or even open biopsy, is indicated. Surgery can provide instant decompression as well as sufficient biopsy material.

The main reasons for misdiagnosis of spinal TB are low incidence, low index of suspicion, declined expertise, and accepted failed biopsy.

CHAPTER 4

Chemotherapeutic treatment for spinal tuberculosis

There is no uniform advise in the literature regarding the duration of chemotherapeutic treatment for spinal tuberculosis. In clinical practice in the Netherlands the duration varies from 6 to >13 months. The aim of the study reported in Chapter 4, was to find out whether a 6 months regimen was equally as effective as a longer treatment regimen (>6 months). Outcome was evaluated in terms of relapse rates after successful treatment.

A review of the literature from 1978 (after the introduction of Pyrazinamide) to 2000 was performed. There were 4 publications with a short-course regimen (2 months ISO, RIF, and PYR followed by 4 months ISO and RYF) with a total of 82 adult patients. All the patients had undergone surgical intervention. The relapse rate was 0%. There were 10 publications with a >6-month regimen of ISO, RIF, and PYR; a total of 274 patients with spinal TB. Surgery was performed in 59% (162/274). Relapse occurred in 2% (4/218).

The relapse rate of 2% for the patients that had > 6 months chemotherapy is low, as is the relapse rate of 0% for patients with 6 months treatment. All the patients who received 6 months chemotherapy had also received surgery. Relapse only occurred in the group that had been treated for longer than 6 months. The fact that surgery was performed for the first group may have contributed to the low rate of relapse, although we know from other studies done before 1978, that there were no statistically significant differences in relapse between operated and control groups. We concluded that the duration of chemotherapy for spinal tuberculosis can be 6 months.

CHAPTER 5

Intralesional penetration of chemotherapy in tuberculosis

Review of the literature revealed that the recommended treatment for almost all forms of tuberculosis, is a short course regimen. There are no separate guidelines for treatment of pleural effusions and psoas abscesses (resulting from spinal TB). Clinical results are generally good, but treatment is not based on real data on intralesional concentrations of these modern drugs. In fact, we do not know if this treatment is truely optimal without insight into drug penetration. This is important since subtherapeutic concentrations may result in selection of a resistant bacterial population and lead to treatment failure.

Chapter 5 reports the results of our study on the concentrations of modern tuberculosis drugs (ISO, RIF, PYR) inside tuberculous pleural effusions and abscesses. Specimens of serum, pleural effusion (6 patients) and psoas abscess fluid (10 patients) were taken by percutaneous drainage 2 h after administration of the drugs, and concentrations were determined.

Intralesional drug concentrations were in the same range for pleural effusions and psoas abscesses. They were below Minimal Inhibitory Concentration (MIC) values in 0/15 patients for ISO, 2/13 for RIF, and 8/9 for PYR. The ratio of the maximal concentration (Cmax) to the MIC is a measure for the potency of a drug; a

Cmax:MIC-ratio >4 is indicative for effectiveness. Cmax:MIC ratio was always >4 for ISO, in 4/13 for RIF, and 0/9 for PYR. In 5/8 patients receiving all three drugs both RIF and PYR had Cmax:MIC ratios <4, indicating intralesional subtherapeutic drug levels.

We concluded that the intralesional penetration of ISO is good, of RIF is intermediate and of PYR is poor. So treatment of patients with pleural effusion and psoas abscesses is not truely optimal given the increased risk of actual monotherapy inside the lesion and subsequent development of resistance. Drainage is advised as additional therapy for patients with pleural effusion or psoas abscesses; it reduces the intralesional bacterial load and shortens the time of resolution of the lesions.

CHAPTER 6

Routine surgery in the treatment of spinal tuberculosis

Chapter 6 concerns the need for surgery. There is controversy in the literature since the 1960's about the necessity of additional surgical intervention in spinal tuberculosis. Potential benefits of surgery are quicker relief of pain, immediate relief of compressed nerve tissue, less kyphosis, and more bony fusion. A Cochrane systematic review was performed with the aim to compare chemotherapy to chemotherapy plus surgery in the treatment of spinal TB.

All relevant studies were identified, and assessed for inclusion. A total of 27 potentially relevant papers were identified of which 22 papers had to be excluded for various reasons. Five publications on two randomised controlled trials (RCT) performed by the British Medical Research Council Working Party on Tuberculosis of the Spine (MRC) were included because they met the inclusion criteria. A total of 331 participants were investigated. The studies were conducted in the 1970s and 1980s with follow-up reports available after 18 months, three years, and five years; one trial also reported 10 years follow up. Completeness of follow up varied at the different time points, with less than 80% of participants available for analysis at several time points. There was no statistically significant difference for any of the outcome measures: kyphosis angle, neurological deficit (none went on to develop this), bony fusion, absence of spinal tuberculosis, death from any cause, activity level regained, change of allocated treatment, or bone loss. Neither trial reported on pain. Of the 130 participants allocated to chemotherapy only, 12 had a neurological deficit and five needed a decompression operation. One trial suggested that an initial kyphosis angle greater than 30° is likely to deteriorate, especially in children.

Data are insufficient to be clear whether chemotherapy plus surgery is better than chemotherapy alone (with surgery used when clinically indicated). The investigated trials were performed some years ago, and current medication and operative techniques are far more advanced. However, these results indicate that routine surgery cannot be recommended unless within the context of a large, well-conducted randomized controlled trial.

Clinicians may judge that surgery may be indicated in subgroups of patients with an initial kyphosis angle greater than 30° (especially in children) or progressive or persistent neurological deficit with spinal cord compression despite chemotherapy but there are no randomized comparisons to support this. Future trials need to assess routine surgery and need to be large enough to assess outcomes properly. They need to assess pain and the patient's view of their disease and treatment. These trials also need to address subgroups of patients with spinal tuberculosis to establish the role of surgery for specific indications.

CHAPTER 7

Prediction of deformity in spinal tuberculosis

The results of the Cochrane review show that the majority of patients with spinal TB can be treated without surgery. There was however, a substantial amount of patients in the review with large or progressed kyphosis at follow up, which are absolute indications for operative correction according to many experts. In chapter 7 we evaluated radiographic and clinical parameters as early predictors for the final kyphosis angle to identify the patients at risk for developing severe or progressive kyphosis.

A retrospective analysis was performed using the archives of Beatrixoord Tuberculosis Center. After strict selection we could include 53 patients with active spinal TB located in the thoracic (T1 to T10) and thoracolumbar spine (T11 to L2), with initial angles < 40 degrees. Clinical and radiological data were obtained and analyzed.

Univariate analysis revealed no significant independent predictors. Multivariate analysis showed that bone loss >0.3 (fraction; 1.0 is a whole vertebral body) in combination with a thoracolumbar localisation indicated 38% chance of non-favourable outcome (progression >10 degrees and/or a final angle >40 degrees) versus only 3% when bone loss was ≤0.3 in combination with a thoracic localisation.

Our aim was to predict which patients are at risk for an unfavourable outcome, but it turned out that we were better in predicting favourable outcome! A simple and clinically useful algorithm for early prediction of kyphosis in spinal TB is presented. We recommend use of the algorithm to improve definition of subgroups to optimise individual treatment.

CHAPTER 10
SAMENVATTING

HOOFDSTUK 1

Inleiding

Tuberculose is een infectieziekte. Een infectieziekte wordt veroorzaakt doordat een ziektekiem het menselijk lichaam binnendringt. De ziektekiem die tuberculose veroorzaakt is de tuberkelbacterie (*Mycobacterium tuberculosis*). Longtuberculose is de meest voorkomende vorm van tuberculose, maar tuberculose kan ook op andere plaatsen in het lichaam voorkomen. Bij vier procent van de tuberculosepatiënten ontwikkelt de ziekte zich in het skelet. De helft van die groep patiënten krijgt tuberculose in de wervelkolom. Wervelkolomtuberculose is een ernstige vorm van tuberculose die het bot aantast (botverlies) en inzakkingen van de wervelkolom kan geven. Dit kan leiden tot bochelvorming en zelfs tot een dwarslaesie door verdringing van het ruggenmerg.

Dit proefschrift geeft een overzicht van wervelkolomtuberculose in Nederland. Het evalueert de huidige diagnosestelling en behandeling van wervelkolomtuberculose en gaat specifiek in op de operatieve behandeling.

Tuberculose was in Nederland in de eerste helft van de vorige eeuw nog een gevreesde ziekte. Jaarlijks eiste deze ziekte 7500 dodelijke slachtoffers. In ontwikkelde landen is het aantal tuberculose gevallen vanaf 1950 geleidelijk afgenomen. Totdat we in het begin van de negentiger jaren van de vorige eeuw wereldwijd een toename zagen. In Nederland zijn nu ieder jaar ongeveer 1400 nieuwe patiënten.

Tegenwoordig hoeft een tuberculose-infectie niet meer dodelijk te zijn. Sterker nog: tuberculosepatiënten in Nederland hebben bijna honderd procent kans om van hun ziekte te genezen.

In ontwikkelingslanden is tuberculose echter nog steeds een levensbedreigende ziekte. Jaarlijks sterven wereldwijd bijna twee miljoen mensen aan tuberculose. Tuberculose veroorzaakt meer sterfte onder volwassenen dan alle andere infectieziekten samen.

HOOFDSTUK 2

Toename van skelettuberculose in Nederland

Alle artsen in Nederland hebben een meldingsplicht voor tuberculose. Het KNCV Tuberculosefonds houdt een zeer gedetailleerd register met al deze gegevens bij. Wij keken naar patiëntengegevens uit de jaren 1993 tot en met 2000 om een analyse te doen van skelettuberculose; hoeveel komt het voor en welke risicofactoren spelen een rol.

Skelettuberculose nam in deze periode geleidelijk toe met in totaal 532 gevallen. Immigranten uit gebieden waar tuberculose veel voorkomt veroorzaakten deze toename. Zij krijgen, bij een gelijk risico op besmetting, vaker skelettuberculose dan

andere bevolkingsgroepen. Dit suggereert dat er erfelijke factoren betrokken zijn bij de manier waarop tuberculose zich uit. Ook vrouwen en ouderen krijgen relatief vaker skelettuberculose.

Een andere belangrijke conclusie van onze analyse is dat een röntgenfoto van de longen waarop geen afwijkingen te zien zijn zeker niet uitsluit dat er toch skelettuberculose in het spel is. Slechts 15% van de skelettuberculosepatiënten heeft ook longtuberculose.

Tot slot constateerden we een lange periode tussen het begin van de ziekteverschijnselen en het stellen van de diagnose, namelijk 32 weken. Deze lange periode wordt zowel door de patiënt als door de arts veroorzaakt. De patiënt komt vaak pas laat bij een arts omdat de ziekte sluipend begint. De ziekte kan langdurig zonder klachten verlopen. Ook de arts heeft vaak veel tijd nodig om de diagnose te stellen. Dit komt mede doordat hij weinig ervaring heeft met de ziekte en er dus niet alert op is. Artsen moeten denken aan skelettuberculose als afwijkingen in het skelet niet direct duidelijk verklaard kunnen worden door een andere ziekte.

HOOFDSTUK 3

Verkeerde diagnose en verkeerde behandeling van wervelkolomtuberculose

Wervelkolomtuberculose wordt regelmatig pas laat of zelfs helemaal niet gediagnosticeerd. Voor de patiënt kan het missen of te laat vaststellen van de diagnose wervelkolomtuberculose ernstige complicaties opleveren. Dit illustreer ik in dit hoofdstuk aan de hand van de ziektegeschiedenis van twee tuberculosepatiënten.

De belangrijkste reden voor de verkeerde behandeling van onze voorbeeldpatiënten is dat de verkeerde diagnose, namelijk kwaadaardig gezwel, werd gesteld. Daarvoor werden ze behandeld met radiotherapie (bestraling). In beide gevallen werd de afwijking groter in plaats van kleiner. Bij nader onderzoek bleek dat deze twee patiënten wervelkolomtuberculose hadden. Eén van de patiënten had verschijnselen van een dwarslaesie die verergerden tijdens de bestraling. Deze dwarslaesie is uiteindelijk niet hersteld. Het is dan ook cruciaal dat de diagnose wervelkolomtuberculose op tijd gesteld wordt. Dan geeft de juiste behandeling de grootste kans op herstel.

Diagnostiek moet altijd beginnen met een grondige anamnese. Bij onze voorbeeldpatiënten is dat niet gebeurd. Bij hen had diepgaander onderzoek eerder de diagnose wervelkolomtuberculose opgeleverd. Het risico om tuberculose te ontwikkelen is veel groter als de patiënt tot een zogenaamde risicogroep behoort. Beide patiënten behoren tot een dergelijke groep. De eerste had in het verleden tuberculose in zijn heup. De tweede was immigrant uit een land waar tuberculose veel voorkomt. Bovendien werd hij met afweer onderdrukkende medicijnen behandeld. Daarnaast zijn in beide gevallen de röntgenfoto's en de botscans onvoldoende goed beoordeeld. Er waren namelijk weldegelijk aanwijzingen te zien voor tuberculose.

De behandeling moet altijd afgestemd zijn op een juiste en sluitende diagnose. Bij onze voorbeeldpatiënten is ook dat niet gebeurd. Bij hen leidde een verkeerde diagnose tot verkeerde behandeling. In beide gevallen is geprobeerd materiaal uit de afwijking te halen met een dikke naald (biopsie) om een goede diagnose te stellen. In beide gevallen bleek er onvoldoende materiaal te zijn voor het stellen van de juiste diagnose. En in beide gevallen is op dit punt het diagnostisch traject gestopt, met als gevolg de start van een verkeerde behandeling gestart. Er had een tweede naald biopsie of zelfs een chirurgische biopsie plaats moeten vinden. Een bijkomend voordeel van een chirurgische biopsie is dat het ruggenmerg ontlast kan worden van de druk die er op zit. Dat vergroot de kans op het verdwijnen van een dwarslaesie.

Het gebeurt vaker dat patiënten met afwijkingen in de wervelkolom radiotherapie krijgen. Zelfs zonder dat hiervoor weefsel uit de afwijking gehaald is om de juiste diagnose te stellen. Het gaat dan meestal om patiënten waarbij gedacht wordt aan een uitzaaiing van kanker. Er wordt dan uitgebreid gezocht naar de meest voor de hand liggende oorzaken van de uitzaaiing: prostaatkanker, borstkanker, longkanker. Als onderzoek één van deze kankers bevestigt dan wordt radiotherapie gestart. Als er geen voor de hand liggende oorzaak gevonden wordt voor de afwijking in de wervelkolom moet er een adequate biopsie volgen. Daarbij moet het weefsel uit de afwijking onderzocht worden op onder andere tuberculose.

HOOFDSTUK 4

Chemotherapie voor wervelkolomtuberculose

Er is geen eenduidig advies in de wetenschappelijke literatuur over de behandelduur van chemotherapie voor wervelkolomtuberculose. In Nederland varieert de behandelduur van zes tot 13 maanden. Dat blijkt uit de gegevens van het Nederlands Tuberculose Register. De behandeling moet lang genoeg zijn, maar niet langer dan nodig. Het is een belastende behandeling met mogelijk bijwerkingen. Doel van deze literatuurstudie is om uit te zoeken of zes maanden behandelduur net zo effectief is als een behandelduur langer dan zes maanden. Deze literatuurstudie laat zien dat voor volwassenen een behandelduur van zes maanden net zo effectief is en dus de voorkeur heeft boven een langere behandelduur.

We hebben de literatuur onderzocht van 1978 tot en met 2000. Vanaf 1978 maakt Pyrazinamide de chemotherapie behandeling van tuberculose duidelijk effectiever. De standaard chemotherapie bestaat uit een combinatie van de medicijnen Isoniazide, Rifampicine en Pyrazinamide. Soms wordt nog Ethambutol toegevoegd.

We vonden vier publicaties met zes maanden behandelduur bij totaal 82 volwassen patiënten. Al deze patiënten werden tevens geopereerd. In alle gevallen was er sprake van een succesvolle behandeling zonder terugkeer van de ziekte bij de laatste controle.

We vonden 10 publicaties met in totaal 274 patiënten die langer dan zes maanden behandeld werden. Van deze groep werden 162 patiënten (59%) geopereerd. Van deze

274 patiënten konden 218 patiënten gecontroleerd worden, 56 patiënten vielen af. In vier van de 218 gecontroleerde gevallen kwam de ziekte terug (2%).

Terugkeer van de ziekte kwam bij zes maanden behandelen en bij langer dan zes maanden behandelen zeer weinig voor. Er lijkt dus geen goed argument te zijn om langer dan zes maanden te behandelen. Alle patiënten die zes maanden behandeld werden, ondergingen ook nog een operatie. Dat zou een factor kunnen zijn die bijdraagt aan het succes van de korte behandelduur. Dit is echter gissen want andere studies laten zien dat er geen verschillen bestaan tussen geopereerde patiënten en niet geopereerde patiënten. Deze studies zijn zelfs van voor 1978, dus nog voordat er betere chemotherapie beschikbaar kwam.

HOOFDSTUK 5

Doordringing van de chemotherapie in longvocht en abcessen bij tuberculose

In het vorige hoofdstuk werd aangetoond dat zes maanden standaard chemotherapie genoeg is als behandeling voor wervelkolomtuberculose. Bij tuberculose kan ook vocht ontstaan in de longen en abcessen in de rugspieren. Er zijn geen aparte richtlijnen voor de behandeling hiervan. De resultaten van de standaardbehandeling zijn meestal goed, ook in geval van longvocht of abcessen in de rugspieren. Tuberculosebehandelaars maken zich echter zorgen over het ontstaan resistentie (ongevoelige tuberkelbacteriën) in dit soort gevallen. Om dit ontstaan van resistentie tegen te gaan moeten dus daadwerkelijk alle tuberculosehaarden in het lichaam met alle drie of vier medicijnen behandeld worden. Dat wil zeggen dat de medicijnen ook tot in het longvocht en de abcessen in de rugspieren moeten doordringen. Er zijn geen eerdere studies gedaan naar de doordringing van de moderne standaard chemotherapie in longvocht of abcessen.

In dit hoofdstuk beschrijf ik de resultaten van onze studie naar de doordringing van de standaard chemotherapie in het longvocht en de spierabcessen. De doordringing van de standaard chemotherapie (Isoniazide, Pyrazinamide en Rifampicine) werd bepaald in zes patiënten met longvocht en 10 patiënten met spierabcessen. Dit gebeurde door met een naald vocht uit de holtes te trekken. Dit werd twee uur na toediening van de medicijnen gedaan. De doordringing (concentratie) van de medicijnen in de vochtophopingen is op dat moment maximaal. De concentraties waren vergelijkbaar in zowel het longvocht als in de spierabcessen.

Er is een minimale concentratie medicijn nodig om de bacterie te doden. Maar een medicijn is pas echt effectief als deze concentratie vier maal zo groot is als de minimaal benodigde concentratie. Deze verhouding was voor Isoniazide altijd goed, maar voor Rifampicine in vier van de 13 gevallen te laag en voor Pyrazinamide in alle negen gevallen te laag. Van de acht patiënten die alle drie de medicijnen kregen waren er vijf die zowel voor Rifampicine als Pyrazinamide te lage concentraties bereikten.

De doordringing van Isoniazide is goed, van Rifampicine matig en van Pyrazinamide slecht. De behandeling van het longvocht en de spierabcessen is dus niet optimaal omdat maar één medicijn goed doordringt en er dus gevaar bestaat op het ontwikkelen van resistentie. Als het medicijn niet goed doordringt in het longvocht of spierabcessen is de behandeling niet optimaal en blijft de infectie bestaan. Een oplossing is dan om het vocht uit de long of het abces af te voeren. Dit geeft een verlaging van het aantal bacillen, vermindert de kans op resistentie en verkort waarschijnlijk ook de genezingsduur. Dit afvoeren van vocht kan door het met een dikke naald weg te zuigen; als dat niet lukt dan kan het met een operatie.

HOOFDSTUK 6

Routinematig opereren in de behandeling van wervelkolomtuberculose

Bijna alle vormen van tuberculose zijn goed te behandelen met standaard chemotherapie. Bij de 1 à 2% patiënten met wervelkolomtuberculose is er echter voortdurend discussie over de noodzaak van een operatie, naast de chemotherapie. Een operatie kan voordelen hebben. Zo kan de pijn sneller verdwijnen. Ook kan een operatie direct druk weghalen op het zenuwstelsel en het ruggenmerg en zo de kans vergroten op het verdwijnen van een dwarslaesie. En door een operatie kan het bot van de aangedane wervels sneller vastgroeien in een betere stand wat weer leidt tot minder bochelvorming.

Het literatuuronderzoek uit dit hoofdstuk is verricht volgens de systematiek van de Cochrane Collaboration. Deze internationale onderzoeksgroep heeft als doel om al het beschikbare bewijs over de effectiviteit van medische interventies samen te vatten in systematische literatuuroverzichten (systematische reviews). Een Cochrane review geeft een overzicht van de resultaten uit primair wetenschappelijk onderzoek en trekt op basis daarvan conclusies over de effectiviteit van een medische interventie.

In deze Cochrane review hebben we gekeken naar de effectiviteit van routinematig opereren. We concludeerden dat er te weinig wetenschappelijk bewijs is (er zijn te weinig patiënten onderzocht) om te kunnen zeggen dat het routinematig opereren gunstig is. De studies zijn gedateerd en er is tegenwoordig betere medicatie en een betere operatie techniek beschikbaar. De behandelend arts kan voor bepaalde groepen patiënten besluiten om weldegelijk een operatie uit te voeren. Toekomstige studies moeten kijken naar deze specifieke groepen en proberen vast te stellen welke patiënten baat kunnen hebben bij een operatie.

In eerste instantie verzamelden we alle studies naar patiënten met werveltuberculose. Vervolgens selecteerden we de studies die een vergelijking maakten tussen de behandeling met alleen chemotherapie en de behandeling met chemotherapie plus chirurgie. Dat leverde 27 artikelen op. Van deze artikelen vielen er nog 22 af omdat zij niet voldeden aan onze strenge criteria. Vijf publicaties voldeden wel. Deze artikelen publiceerden over de resultaten van twee grote studies waarbij

in totaal 331 patiënten werden geanalyseerd. De studies werden gedaan tussen 1970 en 1980. De resultaten worden beschreven na 18 maanden, drie, vijf en 10 jaar. Bij meerdere controlepunten werd minder dan 80% van de groep geanalyseerd. Er werd gekeken naar standsafwijking van de wervelkolom, zenuwuitval, vastgroeien van de wervels, terugkeer van de ziekte, overlijden van de patiënt, terugkeer naar het oude activiteiten niveau, verandering van het ingezette beleid en botverlies.

Er werd voor geen van de onderzochte punten een statistisch significant verschil gevonden. Dat wil zeggen dat er geen bewezen meerwaarde is voor het routinematig opereren van patiënten met wervelkolomtuberculose. Er zijn hier wel enkele opmerkingen bij te maken. Van de groep van 130 patiënten die alleen chemotherapie kreeg waren er 12 die in meer of mindere mate verschijnselen hadden van een dwarslaesie. Van deze 12 personen zijn er vijf toch geopereerd om de dwarslaesie op te heffen. Verder bleek uit één van de studies dat een standsafwijking van de wervelkolom groter dan 30° waarschijnlijk toe zal nemen, vooral bij kinderen.

HOOFDSTUK 7

Voorspellen van de standsafwijking van de wervelkolom (bochel) bij tuberculose

Het vorige hoofdstuk liet zien dat er niet genoeg bewijs is voor de effectiviteit van routinematig opereren van patiënten met wervelkolomtuberculose naast de standaard chemotherapiebehandeling. Er zijn echter aanwijzingen gevonden dat voor bepaalde patiënten opereren mogelijk wel effectief zou zijn geweest om een grote standsafwijking te voorkomen. Een standsafwijking wordt gemeten in graden. Afwijkingen groter dan 40° zien we als indicatie om te opereren omdat de kans groot is op ontwikkeling van pijn en zelfs neurologische uitval. Ook zien we dan vaak een verdere toename van deze grote standsafwijkingen.

In dit hoofdstuk kijken we of we in een vroeg stadium van de ziekte kunnen voorspellen welke patiënten uiteindelijk een operatie nodig hebben vanwege een verslechtering in de standsafwijking. Een operatie in een vroeg stadium van de ziekte is voor deze patiënten veiliger en effectiever en voor de arts beter uit te voeren. We definiëren een verslechtering als een toename van de standsafwijking met meer dan 10° of een uiteindelijke standsafwijking groter dan 40°. Onze studie laat zien dat botverlies en plaats van de werveltuberculose bruikbaar zijn om het risico op verslechtering van de standsafwijking te voorspellen.

We onderzochten een groep patiënten uit het archief van UMCG Beatrixoord, het behandelcentrum voor tuberculose. We evalueerden de röntgenfoto's en medische dossiers van alle patiënten met wervelkolomtuberculose. Van deze groep selecteerden we 53 patiënten met een standsafwijking kleiner dan 40°. Deze groep analyseerden we nader op factoren die een rol zouden kunnen spelen bij verslechtering van de standsafwijking. We keken onder andere naar leeftijd, geslacht, botverlies, medicijngebruik, plaats van de aantasting en aantal aangetaste wervels.

Statistische analyse toont aan dat bij mensen met een beperkt botverlies in combinatie met werveltuberculose in de borstwervelkolom, de kans op verslechtering zonder operatie zeer klein is (3%). De kans op verslechtering van de standsafwijking is beduidend groter (38%) als het botverlies groter is en de tuberculose in het overgangsgebied zit tussen borst- en lendenwervels.

Op basis van deze studie adviseren we alle patiënten met een standsafwijking kleiner dan 40° aanvankelijk zonder operatie te behandelen tenzij ze een dwarslaesie hebben. We raden aan patiënten met veel botverlies en een aantasting in het overgangsgebied tussen borst- en lendenwervels nauwgezet te volgen. Dan kan op tijd geopereerd worden om verdere verslechtering tegen te gaan.

We ontwikkelden een methode die het risico op verslechtering van de standsafwijking voor een patiënt voorspelt (Tabel 1). Deze methode is simpel en bruikbaar en draagt bij aan een verdere optimalisatie van de behandeling van de individuele patiënt.

Tabel 1

Kans op verslechtering van de standsafwijking voor alle combinaties van de twee best voorspellende factoren: botverlies en plaats van de aantasting.

veel botverlies (>0.3)*	overgangsgebied borst- en lendenwervelkolom aangetast	kans op verslechtering van de standsafwijking
ja	ja	38%
ja	nee	19%
nee	ja	7%
nee	nee	3%

* 1,0 botverlies = 1 volledige wervel verlies

APPENDICES

THANKS TO MANY

As a writer, I would not have had any success. My childhood was a happy one, not a writer's goldmine. I was born in Zaandam on August 12 1966. Two and three years later my brother Vincent and my sister Ellen were born. We moved to the East and lived in Gorssel for many years. The first school years I spend in Joppe, between the monkeys and dears in a forest school. My high school (Geert Groote College, Deventer) was a decent old fashioned institute, a good preparation for university. After not being admitted to study Medicine, I started in Nijmegen with Health Sciences. The next year (1986), I was luckier and I was permitted to study Medicine. Being a student was great, I felt on top of the world. I met Marieke during these years and after my theoretical graduation (1992) we moved to Amsterdam. I finished my doctors' exam there in 1995. My father was a designer and my mother a nurse, so I inherited a bit of both and wanted to become an orthopaedic surgeon.

I started working on the orthopaedic department of Professor Paul Wuisman, Free University Medical Center. He helped me with my first scientific experiences and publications during my study and my first real job. This certainly aided in getting a traineeship. We worked together for two years before the general surgery part of my training started.

My traineeship would take place in the Northern region. In the beginning of my residency in general surgery, I learned surgical theory and skills. The surgeons at the Deventer Hospital (captained by dr Eeftinck Schattenkerk) provided a thorough training. Long working hours and loads of shifts took all my intellectual and physical capacity. Pressure was high and all efforts were focused on survival of patients and residents. It was a though learning process in which I experienced a huge personal and professional growth. Thanks to my wife Marieke, I kept the good spirit. On the other hand I lost 10 kg. We got married during this period.

After this period I started my orthopaedic training in Zwolle, in the Isala Clinics Location Weezenlanden. An excellent environment for general orthopaedic training. A good framework gave me the opportunity for both theoretical and practical training. I found the close collaboration of orthopaedic and general surgeons an example of how both disciplines can profit from each others expertise. It was during this year (2000) that I started working on my thesis on bone and joint tuberculosis. It began with a little post-it memo in my file in the depths of the personal archives of Professor Jim van Horn. It spelled 3 letters: TBC. We had a conversation in which he proposed that I started working on a thesis on bone and joint tuberculosis. I would work on it together with Richard van Altena, pulmonologist and TB-expert at Tuberculosis Center Beatrixoord of the University Medical Center Groningen (UMCG).

I admit that at first sight I was reluctant to start research on this topic. It felt a bit awkward to study a subject that was so uncommon in the Netherlands. Van Horn convinced me that it would be extremely interesting and so I started. At first I felt a bit lonely. There was no large laboratory or center of expertise supporting and guiding my efforts. René Castelein reversed this believe. He stated that it was a big advantage to be able to make my own plans and take my own decisions. It would really be my project. His words motivated me to go on.

Working with Richard van Altena turned out to be really satisfying in many aspects. His professional skills and his sense of humour are quite unique. During this period I started to work together with Joke van Loenhout, a pulmonologist from Nijmegen. We shared the same interest in spinal tuberculosis. This proved to become a pleasant and successful cooperation. Later this year a unique event took place, I became a father. Our beautiful daughter Sara was born, a real summer child!

The second part of my residency took place at the Deventer Hospital. In this period I was given a lot of freedom in my work. It gave me real confidence to be trusted that much. During this time, I learned a lot about practical parts of the job and institutional aspects. During my period in Deventer Dré Driessen had his own way of providing a stimulus for science. On a regular basis he just asked me about the progress I made. Was it the guilty feeling he provoked when the progression had been minimal? He also facilitated the research by permitting me every now and then to go to Beatrixoord to work on my thesis.

I also started with a Cochrane Systematic Review together with Joke. A lot of work from which I learned many things. The support of Harriet, Reive and Professor Paul Garner was invaluable to finish this large project. Their guidance during my weeks visit to the Liverpool School of Tropical Medicine was excellent.

The last part I spent at the UMCG. I was not very eager to 'go academic', since peripheral hospitals had been so much fun. However, it proved to be a very stimulating and inspiring place to work. So when Jim van Horn asked me to become a member of his staff, it felt good. It gave me the opportunity to go on with all aspects of the academic profession I like so much: patient care, education, training and research.

We had hardly moved to Groningen when our second summer child was born: Willem. It was a turbulent period. At that time I started working on chapter seven with Sander Wuite and Bertram The. That was the dustiest period of this thesis, especially for Sander who worked his way through many patient files. Bertram showed us his methodological talents. We had a lot of fun during the years we worked together.

My last year as a resident was preparing me for my future field of interest. I was granted a fellowship in orthopaedic oncology at the Rizzoli Institute in Bologna. Furthermore I was scheduled out of clinical work for two months to work on my thesis. We left to Italy in August 2003 and came back in December. The Italian experience was quite unique for all of us. Professor Mario Mercuri proved to be an excellent surgeon and a good clinician and teacher. I saw many new technologies, innovative approaches and met a lot of interesting new friends. With Eric, Max and Costa I spend many hours in the antique archives doing research. Our family, the dog included, saw the grapes being harvested, enjoyed the fine food and wines and specifically the friendliness of Italians and the city of Bologna. Willem started walking there, downhill.

From the end of 2003 my residency was finished and I became responsible for the orthopaedic oncology in our hospital with initial back-up from Jim van Horn. It is quite a step from resident to staff with all responsibilities. But my colleagues provided an environment of knowledge and support. In 2005 another summer child was born, our youngest son Dirk. A real charmer and night owl who is hugged to pieces by his older brother and sister.

In our setting at the moment we treat several patients each year with spinal tuberculosis. We work in a multidisciplinary team consisting of Richard van Altena, Maarten Coppes, Albert Veldhuizen and myself. Orthopaedic oncology is another multidisciplinary field, demanding but very rewarding. At present our department is changing its culture. Furthermore, the hospital is changing its organisation. I started working as Chef de Clinique in October 2005. Being part of the management team is dynamic and takes a lot of time.

The last few months I worked very hard to finish my thesis. Thanks to the creativity of Anne Koningsberger and Karin van Duijnhoven my thesis got its beautiful look. It is great that I can return the favour of being paranimf to my good friend Bas van den Borne. Maybe one day my other paranimf and friend Paul Heiden returns this favour to me...

I love my family Marieke, Saar, Willem and Dirk. I'm proud of them.

The thesis is finished now and looking back I realise that it has been a privilege to live and work together with so many talented and inspiring people.

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