INTRODUCTION
Although nasopharyngeal cancer (NPC) is rare in the West, it is a common cancer of the head and neck in the Chinese population. The global incidence of NPC is 1.3 per 100,000, with more than 80,000 new cases diagnosed in 2008. In Singapore, the incidence of NPC in 2008 was 7.7 per 100,000, with 354 new cases diagnosed. Thus, the number of NPC patients is significant.

The primary treatment for NPC is radiotherapy (RT). Although it has been shown to have good tumour control and overall survival rates, there are some associated side effects. Osteoradio-necrosis (ORN) may occur in bony structures within the treated RT field that receives a high radiation dose. These include the clivus, temporal and occipital bones, the atlas (C1) and the axis (C2). The estimated incidence of ORN has been found in some studies to be as high as 1% in NPC patients treated with RT. King et al found that out of 884 NPC patients studied, nine had C1/2 changes due to ORN. Superimposed acute or chronic infection of the prevertebral tissue and C1–2 vertebrae can occur with polymicrobial organism involvement. ORN and superimposed infection may damage C1–2 structural integrity, leading to C1–2 instability and cord compression with loss of neurological function.

There has been limited literature on the surgical management strategies of C1–2 involvement in NPC patients, with only four reported cases found in the literature. We review our experience with three cases of NPC with C1–2 instability and the medical/surgical treatment strategies employed, along with a review of the current literature.
in both directions. The flexion/extension cervical radiographs showed C1–2 subluxation (the atlanto-dens interval [ADI] was 4 mm, the normal in adults being less than 3 mm on flexion) (Figs. 1a & b). Computed tomography (CT) of the cervical spine showed basilar invagination, with the tip of the odontoid process telescoping superiorly into the foramen magnum (Fig. 1c). Axial CT image (Fig. 1d) showed the tumour invading into the left side of the anterior arch and the lateral mass of C1. Magnetic resonance (MR) imaging of the cervical spine showed an enhancing tumour invading from the left posterior nasopharynx into the left lateral mass of C1 and also the C2 body/dens (Figs. 1e & f). There was no evidence of cervical cord compression, and the C1–2 instability was attributed to direct tumour invasion. The patient underwent occipitocervical fusion (occiput C3–4) and was discharged subsequently for further palliative therapy.

**Patient 2: C1–2 osteomyelitis with instability**

A 63-year-old Chinese woman was diagnosed with T2N1M0 undifferentiated NPC in 1996. Using a similar technique as for Patient 1, she received conventional external beam RT of 66 Gy in 33 fractions. This was followed by an intracavitary boost of 10 Gy (two insertions of 5 Gy each, one week apart). In 1997, the patient developed a C1–2 cervical abscess and underwent
anterior cervical surgical drainage, followed by a course of antibiotics. She was well until 2010 when she developed C1–2 osteomyelitis. Posterior nasopharyngeal space (PNS) biopsy revealed acute and chronic inflammation with no tumour recurrence. The microbial cultures showed Staphylococcus, Streptococci and Candida. Tuberculosis culture was negative. She was treated with antibiotics and antifungals, and responded well to the treatment.

The patient was re-admitted in July 2011 for neck pain on movement of one month’s duration, accompanied by limb numbness. On physical examination, there was a severe decrease in the cervical range of motion. Both flexion and extension were only 20 degrees. Rotation was 10 degrees in each direction. Torticollis was present and the patient’s neck was tilted to the left. Reflexes in the upper and lower limbs were not increased, and limb power was graded 4/5 in all limbs. There was no sensory loss and she was able to ambulate. Her blood investigations showed a normal C-reactive protein of 5.7 mg/L, and erythrocyte sedimentation rate was 50 mm/hour. The total white cell count was normal at 7.17 × 10^9/L, as was the differential cell count.

MR imaging of the cervical spine showed basilar invagination. The tip of the odontoid process had gone above McRae’s line (the line joining the anterior to the posterior margin of the foramen magnum). There was also C1–2 subluxation (the ADI was more than 3 mm), with compression of the cervicomedullary junction (Figs. 2a & b). Destruction of the anterior arch of C1, odontoid process and contrast enhancement were noted. There was no localised abscess. On the coronal images, there was a lateral tilt of the skull to the left (Fig. 2c). On CT imaging, osteolytic permeative changes in the skull base bones, suggestive of ORN, were observed.

The patient was diagnosed with C1–2 chronic osteomyelitis in the background of ORN with craniocervical instability. She underwent a transoral, transpharyngeal wall biopsy of the C2 bone. The microbial cultures grew Streptococcus (Group B), Staphylococcus aureus and Candida (glabrata and krusei). Histology showed no tumour recurrence. The patient was treated with a course of antibiotics consisting of vancomycin (dosage 750 mg twice a day for six weeks), which was later changed to linezolid (dosage 600 mg twice a day for six weeks). The antifungal drug used was voriconazole (dosage 200 mg for six months), as per the recommendations by the infectious disease specialists. Subsequently, after the infection was treated, she underwent an occipitocervical fusion to address the craniocervical instability. The instrumentation consisted of an occipital plate-rod construct, together with C3,4,5 lateral mass screws (Fig. 2d). A C1 posterior arch laminectomy was also done to decompress the cervicomedullary junction. During this surgery, intra-operative neurophysiological monitoring was used. Motor-evoked potentials (MEPs) were monitored during the positioning of the patient’s neck and during the surgical decompression to ensure that no damage to the spinal cord occurred.
Patient 3: C1–2 abscess with C2 pathological fracture and instability

The patient was a 66-year-old Chinese woman who was diagnosed with T2N0M0 undifferentiated NPC. In February 2010, she received IMRT, delivered at 69.96 Gy in 33 fractions. Her radiation treatment plan and dosimetry are shown in Figs. 3a & b. In March 2011, the patient developed a local recurrence and underwent a nasopharyngectomy. A month later, she presented with neck pain and stiffness associated with fever lasting one week. On physical examination, a decrease in her cervical range of motion was noted. Flexion, extension and rotation were all 45 degrees. No limb weakness or sensory loss was detected. Reflexes in the upper and lower limbs were normal. Hoffman’s sign was negative. Her blood investigations showed an elevated C-reactive protein of 274 mg/L (normal 0.2–8.8 mg/L). Her white blood cell count was normal at 9.32 × 10^9/L (normal 4–10 × 10^9/L). However, the white cell differential count showed an elevated neutrophil count of 84.5% (normal 40%–75%). The erythrocyte sedimentation rate was elevated at 121 mm/hour (normal 3–20 mm/hour).

Cervical MR imaging showed a retro-odontoid collection, which was rim-enhancing with contrast (Figs. 3c & d). There was spinal canal stenosis and increased T2 spinal cord signal due to oedema (Fig. 3e). There were mild degenerative cervical spondylotic changes at other levels. CT of the cervical spine showed a C2 fracture (Type II Anderson and D’Alonso) (Fig. 3f) and pockets of air in the retro-odontoid soft tissue. The patient was diagnosed with a retro-odontoid abscess and C2 pathological fracture with instability. It is unlikely that she had ORN, as the radiation dose to the spine was relatively low (< 55 Gy), the time...
interval from RT was relatively short, and her symptoms occurred soon after the nasopharyngectomy.

The patient underwent transoral drainage of the abscess by drilling through the body of C2. Fig. 3g shows the bone removal in C2. Intra-operatively, frank yellow-coloured pus was drained and the microbial cultures showed Staphylococcus aureus, Enterobacter and Candida tropicalis fungi. The patient was started on the appropriate antibiotics: intravenous vancomycin (1 g twice a day for three months), cefepime (2 g three times a day for three months) and fluconazole (400 mg once a day for three months). Her inflammatory markers subsequently decreased to normal. After the full duration of antibiotics, she underwent occipitocervical surgical fixation (occupit C3–4) to address her cranio-cervical instability. For instrumentation of C4, she had one pedicle screw inserted into the larger pedicle. Cervical pedicle screws are longer than lateral mass screws and offer a higher biomechanical strength. They can only be inserted when the patient’s pedicle is wide enough. The other three screws in C3,4 were standard lateral mass screws. The patient was discharged well and pain free, with no neurological defects.

DISCUSSION

The estimated incidence of ORN has been found in some studies to be as high as 1% in NPC patients treated with RT. King et al.[7] found that out of 884 NPC patients studied, nine had C1/2 changes due to ORN. The risk factors for ORN were found to be additional RT, either in the form of brachytherapy, stereotactic RT or an RT boost. Patient 2, who had ORN, had the risk factor of intracavitary brachytherapy. The classical diagnostic features of ORN on MR imaging include C1/2 vertebral marrow changes with a narrow zone of transition between normal and abnormal marrow. This demarcation is due to the field of radiation therapy delivered. The anterior elements of C1, consisting of the anterior arch and lateral masses, are involved with sparing of the posterior arch. In C2, the odontoid process and the vertebral body are involved, but the lamina/spinous process are spared.[5] On CT images, C1/2 bone changes include sclerosis or osteolysis.[5]

The differential diagnosis in NPC patients would be osteomyelitis or local tumour recurrence. The likelihood of the aetiology being direct tumour invasion is higher if the patient has had a prior local recurrence (as was the case in Patient 1). In such patients, the MR imaging would show contiguous tumour invasion from the PNS into C1–2. Diagnosis can be difficult occasionally, and surgical transoral biopsies are sometimes necessary to differentiate the various pathology.

In NPC patients, the retropharyngeal soft tissue, together with the C1–2 bone, is at risk of infection, as RT can affect vascular supply to the tissues, resulting in a hypoxic environment.[6] Pharyngeal surgery in this environment is a risk factor for C1–2 postoperative infection. During nasopharyngectomy, the normal anatomical barrier between the nasopharyngeal cavity and the C1–2 bone may be breached. The normal microbial flora of the pharyngeal cavity, which includes Staphylococcus, Streptococcus and fungal Candida, can then cause acute or chronic infection,[1] as was seen in Patient 3. The infection in this patient resulted in a C2 pathological fracture and instability. ORN is unlikely to have occurred, as it had only been one year post RT and the radiation dose received by the spine was kept relatively low with IMRT. The mainstay of treatment for infection is antibiotic therapy guided by microbial cultures. Surgical drainage is required when there is significant compression of the spinal cord with neurological deficits. Occasionally, combined surgical approaches are required for treatment, i.e. transoral decompression followed by posterior fixation.

Radiation may damage the bony joints of C1–2 and also the ligamentous structures. The most important ligament involved in C1–2 stability is the transverse ligament of C1. Damage to this or the odontoid process itself predisposes to subluxation of the C1 arch anteriorly. The C1–2 facet joint capsules, if damaged, may also lead to subluxation. The diagnosis of C1–2 subluxation is made when the ADI is more than 3 mm on dynamic flexion and extension radiographs. The normal ADI in adults is less than 3 mm. An increase in ADI is seen in the dynamic cervical radiographs of Patient 1. This can eventually lead to cervicomedullary neural compression and damage, which would result in the patient presenting with neck pain. Patient 1 developed C1–2 instability due to direct tumour invasion. The tumour invaded and gradually destroyed his bony/ligamentous C1–2 stabilising joint structures. Patients may also present with symptoms and signs of a high cervical myelopathy. These would include weakness and numbness of all four limbs. Commonly, patients would present with clumsy hands, difficulty buttoning their clothes and an unsteady gait.

If the pathology progresses and the C1–2 instability is not treated, the patient may develop basilar invagination. This occurs when the atlanto-occipital joints are damaged, and the odontoid process/C1 telescopes vertically into the foramen magnum (Patients 1 & 2). Radiological diagnosis is made when the tip of the odontoid process has gone above McRae’s line. Once cranio-cervical instability has occurred with spinal cord compression, surgery should be considered. The aims of surgery are to decompress the neural elements and stabilise the cranio-cervical junction. In all three of the above cases, occipitocervical fusion instrumentation was performed. The C1/C2 vertebrae were all unhealthy and unsuitable for C1–2 fixation. In the presence of basilar invagination or unhealthy C1–2 vertebrae, an occipitocervical fixation is necessary. This, however, has the unfortunate side effect of significantly decreased neck range of motion.

Surgical challenges in NPC patients include abnormal anatomy or alignment of the occipital and C1–2 bones. Malplacement of screws may occur, causing injury to the spinal cord or vertebral artery. The cervical pedicle and vertebral artery anatomy may also vary. Tomasinio et al.[7] found that in up to 23% of cases, abnormal cervical anatomy was present (such as
narrowed pedicles and split or twisted vertebral artery). As such, we minimised the surgical risks by using various aids. One such aid we routinely utilise is spinal navigation. This is a CT-based computer image guidance system that helps the surgeon plan the location of the entry points of the screws, thus avoiding screws breaching out of the bone, which may damage vital neurovascular structures. This method has been shown to increase safety in spinal instrumentation. Spinal instrument navigation was used in all three of our patients, with good results. There was no screw malplacement causing damage to vital structures. Another benefit of using navigation is in obtaining screw purchase in the thickest part of the occipital bone. The more lateral squamous parts of the occiput are composed of flatter bone and do not afford as good a screw purchase as the thick midline keel of bone. Also, if the midline screw is inserted too superiorly, there is a risk of damage to the torcula (confluence of venous sinuses within the intracranial dura), which can result in significant extradural haemorrhage. By using navigation, the ideal occipital screw entry point into the midline occipital bone can be determined.

Another tool that we use in enhancing the safety of NPC patients undergoing surgery is intra-operative neurophysiological monitoring. This has been shown to be helpful in preventing neurological injury during cervical spine surgery. We regularly monitor the MEP and somato-sensory evoked potentials. If significant drops in potentials occur, the surgeon is alerted and can then look for possible causes of spinal cord compression such as incorrect neck positioning, and correct the problem immediately. During the induction of anaesthesia, excessive manipulation of the neck is avoided, and techniques such as fibre-optic awake intubation are utilised. Neutral cervical spine alignment is also maintained during the process of patient positioning and surgery. Just prior to surgery, a fluoroscopic radiographic image is used to confirm good craniocervical alignment, which would avoid spinal cord compression. Using such surgical aids and anaesthetic techniques, a good surgical outcome can be obtained.

CONCLUSION
NPC patients are at risk of developing high cervical pathology, such as ORN, osteomyelitis and direct tumour invasion. These can result in craniovertebral junction instability with cervical spinal cord compression. Diagnostic aids include serum inflammatory markers, transoral biopsies and MR imaging/CT radiology. Surgical treatment with various intra-operative aids, such as spinal navigation and intra-operative neurophysiological monitoring, can ensure a safe outcome. A multidisciplinary team, consisting of the radiation oncologist, infectious disease specialist, surgeon, physiotherapist and rehabilitation physician, can also optimise the outcome.

REFERENCES