

Elective neck dissection benefits patients with early stage oral cancer

A randomized trial was performed involving patients with stage T1/T2 NO oral cancer, who had their tumour resected either with or without elective neck dissection (<https://doi.org/10.1038/s41416-019-0587-2>). Guidelines remain unclear over whether these patients benefit from upfront elective neck dissection, particularly those with the smallest tumours. Data were also collected from a concurrent cohort of patients who had their preferred surgery. End points included overall survival and disease-free survival.

The study involved 250 randomized and 346 observational cohort patients. Occult neck disease was found in 19.1% (T1) and 34.7% (T2) patients respectively. Elective neck dissection was effective for small tumours. Patients who had elective neck dissection experienced more facial and neck nerve damage, but quality of life was largely unaffected. The observational cohort supported these findings.

Perioperative covert stroke in patients undergoing non-cardiac surgery

A prospective cohort study was performed in 12 academic centres in nine countries, assessing patients aged 65 years or older who underwent inpatient, elective, non-cardiac surgery and had brain magnetic resonance imaging after surgery ([https://doi.org/10.1016/S0140-6736\(19\)31795-7](https://doi.org/10.1016/S0140-6736(19)31795-7)). Multivariable regression was used to explore the association between covert stroke and the primary outcome of cognitive decline.

Among patients who completed the 1-year follow up, cognitive decline 1 year after surgery occurred in 29 (42%) of 69 participants who had a perioperative covert stroke and in 274 (29%) of 932 participants who did not have a perioperative covert stroke. Covert stroke was also associated with an increased risk of perioperative delirium and overt stroke or transient ischaemic attack at 1-year follow up.

Joint annual census of physicians highlights workforce crisis in NHS

The Royal College of Physicians of Edinburgh, the Royal College of Physicians and Surgeons of Glasgow, and the Royal College of Physicians of London have released the results of the latest annual census of physicians in the UK (https://www.rcpe.ac.uk/sites/default/files/census_2018_executive_summary_0.pdf).

The census reveals the continuing pressures on the medical workforce and NHS systems. These pressures are demonstrated by ongoing problems with rota gaps, unfilled posts and high levels of reported sickness absence. Once again, the census shows that the number of posts needed across the system significantly outnumbers the supply of physicians.

Key findings of this year's census include 40% of consultants and 63% of higher specialty trainees saying that rota gaps occurred on a daily or weekly basis. Only 7% and 12% respectively said such gaps did not lead to significant patient safety issues.



Professor Derek Bell, President, Royal College of Physicians of Edinburgh

Of higher specialty trainees 55% reported that they had felt pressured to cover rota gaps and 26% said they were encouraged to take on the work of more than one doctor almost always or most of the time when covering a gap. A finding of note is that in the next 10 years, 36% of consultants will reach their planned retirement age.

Speaking about the results, Professor Derek Bell, President of the Royal College of Physicians of Edinburgh, said: 'The census –

once again – highlights the immense pressures that exist in the NHS across the UK with rota gaps, unfilled posts and high levels of sickness absence all having a significant impact on our medical workforce and, ultimately, patient safety.

He emphasized: 'It is time to value our medical workforce and support their wellbeing to retain the experience, skills and knowledge of doctors at every level, from trainees to senior consultants.'

Type of anaesthesia has no influence on the risk of breast cancer recurrence

A large-scale international study has shown that, despite recent concerns, the use of general anaesthesia does not carry any increased risks of breast cancer recurrence compared to regional anaesthesia.

The study – one of the largest in anaesthesia – was conducted over 10 years and included more than 2000 women undergoing curative breast cancer surgery ([https://doi.org/10.1016/S0140-6736\(19\)32313-X](https://doi.org/10.1016/S0140-6736(19)32313-X)). Participants were followed up at regular intervals for several years – median follow up was 36 months. Regional anaesthesia, while causing less postoperative pain and nausea, was found to have no advantages over general anaesthesia in terms of recurrence of breast cancer.

'This should help to counteract the recent concerns against using opioids in anaesthesia,' says Dr Edith Fleischmann of the Department of Anaesthesia, Critical Care and Pain

Medicine at the Medical University of Vienna, who led the study alongside her colleague Dr Peter Marhofer. 'We were able to disprove the theory that anaesthesia has a negative impact on tumour growth in breast cancer.'

The researchers emphasized the clinical significance of these findings, with Dr. Marhofer explaining: 'both general anaesthesia and regional anaesthesia are safe anaesthesia methods with very few side-effects and complications.'

However, they also noted the need for future trials investigating the effects of anaesthesia on more complex operations, such as curative surgeries for prostate or colorectal cancer. To Dr Fleischmann, the study demonstrates 'the importance of clinical trials to validate or – as in this case – refute the results of in vitro and animal studies.'

Isobel Clough

Study finds link between levels of sex hormones, obesity and likelihood of having asthma

The first population-based study of sex hormones and asthma in both men and women has discovered a link between hormone levels, obesity and asthma.

The study analysed information from 9238 American adults and found that individuals with elevated serum levels of oestradiol and free testosterone were less likely to have asthma (<https://doi.org/10.1164/rccm.201905-0996OC>).

This link was especially pronounced in obese women, whose odds of having asthma were 57% higher if their levels of oestradiol were in the lowest quartile compared to the highest quartile. Low levels of testosterone also raised the likelihood of asthma in this population. Among non-obese men, the association between sex hormones and asthma was still significant; low levels of



Dr Juan Celedón, Niels K. Jerne Professor of Pediatrics and Medicine, University of Pittsburgh, Pittsburgh, Pennsylvania, USA

oestradiol were associated with a 56% higher likelihood of asthma.

‘Our study results suggest that the circulating sex hormones oestradiol and free testosterone contribute to sex differences in asthma among adults,’ said senior author Dr Juan Celedón, chief of pulmonary medicine at UPMC Children’s Hospital in Pittsburgh, USA. ‘Furthermore, obesity appears to modify the effect of such hormones on asthma in women and men.’

However, the exact nature of the link between sex hormones, obesity and asthma remains unclear. As the present study was cross-sectional, it cannot determine whether sex hormone levels could cause asthma, nor vice versa. The researchers therefore emphasized the need for longitudinal studies to further investigate this link.

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Effect of early postnatal transfer and birth outside a tertiary hospital on outcomes in very preterm infants

An observational cohort study was carried out to determine if postnatal transfer or birth in a non-tertiary hospital is associated with adverse outcomes (<https://doi.org/10.1136/bmj.15678>).

Extremely preterm infants born at less than 28 gestational weeks between 2008 and 2015 were grouped based on birth hospital and transfer within 48 hours of birth: upward transfer (non-tertiary to tertiary hospital), non-tertiary care (born in non-tertiary hospital, not transferred), and controls (born in tertiary hospital, not transferred). Infants were matched on propensity scores and predefined background variables. The main outcome measures were death, severe brain injury, and survival without severe brain injury.

A total of 2181 infants (727 from each group) were well matched. Compared with controls, infants in the upward transfer group had no significant difference in the odds of death before discharge but significantly higher odds of severe brain injury and significantly

lower odds of survival without severe brain injury. Compared with controls, infants in the non-tertiary care group had significantly higher odds of death but no significant difference in the odds of severe brain injury or survival without severe brain injury. Compared with infants in the upward transfer group, infants in the non-tertiary care group had no significant difference in death before discharge but significantly lower odds of severe brain injury and significantly higher odds of survival without severe brain injury. No significant differences were found in outcomes between the horizontal transfer group ($n=305$) and controls ($n=1525$).

In extremely preterm infants, birth in a non-tertiary hospital and transfer within 48 hours are associated with poor outcomes when compared with birth in a tertiary setting. The authors recommend that perinatal services promote pathways that facilitate delivery of extremely preterm infants in tertiary hospitals in preference to postnatal transfer.

Proportion of people over 65 years taking antidepressants more than doubles in two decades

The proportion of people over 65 years of age taking antidepressants has more than doubled in two decades (<https://doi.org/10.1192/bjp.2019.193>), found the Cognitive Function and Ageing Studies. However, there was no evidence for a change in age-specific prevalence of depression.

Tuberculosis still leading global infectious killer

The World Health Organization’s Global Tuberculosis Report 2019 (<https://www.who.int/tb/global-report-2019>) finds that tuberculosis remains the leading global infectious disease killer. World Health Organization data shows that while deaths from tuberculosis declined slightly, from 1.6 million in 2017 to 1.5 million in 2018, the number of new tuberculosis cases remained steady at about 10 million in both 2017 and 2018.

Patients with depression, anxiety or stress are more likely to drop out of cardiac rehabilitation

A retrospective study has found that patients with moderate symptoms of depression, anxiety or stress were significantly more likely to quit cardiac rehabilitation than those with no or mild symptoms (<https://doi.org/10.1177/2047487319871716>).

Crohn's disease study identifies genetic variant with potential to personalise treatment

An observational study involving UK-wide collaboration has demonstrated that a genetic variant explains why some patients develop antibodies against the anti-tumour necrosis factor (TNF) drugs, infliximab and adalimumab, and lose response (<https://doi.org/10.1053/j.gastro.2019.09.041>).

Anti-TNF drugs are used to treat patients with moderate to severe Crohn's disease and ulcerative colitis when other treatments have not worked.

The Personalised anti-TNF therapy in Crohn's disease study (PANTS) looked at the clinical data and genetics of 1240 patients with Crohn's disease starting anti-TNF treatment at 120 UK hospitals. Significant association signals were confirmed in a replication cohort of 178 patients with inflammatory bowel disease. This identified a genetic marker HLA-DQA1*05, carried by 40% of the European population, that increases the risk of development of antibodies against infliximab and adalimumab 2-fold.

The authors concluded that a further trial is required to confirm that genetic testing before treatment will reduce the rate of treatment failure by facilitating the most effective choice of therapy for individual patients.

Real-world study finds higher discontinuation rates for lumacaftor-ivacaftor than previously reported

Adverse side effects of lumacaftor-ivacaftor (Orkambi) may be causing higher discontinuation rates among patients with cystic fibrosis than previously reported.

The combination drug was approved in 2015. However, in a real-world study of 845 participants from 47 different treatment centres in France, Dr Pierre-Régis Burgel and colleagues found that 18.2% of patients were unable to tolerate the drug for a full year (<https://doi.org/10.1164/rccm.201906-1227OC>).

This was a markedly higher discontinuation rate than reported in previous clinical trials, in which less than 5% of patients discontinued the combination therapy, even among patients with milder forms of cystic fibrosis. Discontinuation rates in patients with milder disease were also three times higher than in clinical trials, presumably because these patients had less stable disease.

The study's 1-year follow up found that nearly half the participants who discontinued lumacaftor-ivacaftor had experienced adverse respiratory events while taking the drug. Meanwhile, a quarter had experienced other



Dr Pierre-Régis Burgel, Professor of Respiratory Medicine, French National Reference Center for Cystic Fibrosis, Cochin Hospital and Paris Descartes University, Paris, France

intolerable side effects, usually involving digestive problems.

However, the study also found that those who could tolerate the drug showed significant improvements in their condition, including an increase in lung function and weight gain of approximately 2–3 kg. This group of patients also had a 35% reduction in courses of intravenous antibiotics.

'For patients who are able to continue lumacaftor-ivacaftor, there is clinically meaningful improvement in respiratory disease and nutritional status,' said Dr Burgel, Professor of Respiratory Medicine,

French National Reference Center for Cystic Fibrosis, Cochin Hospital and Paris Descartes University, Paris, France.

Yet previous clinical trials may have significantly overestimated the suitability of the drug for the general population of patients with cystic fibrosis. Dr Burgel explains that, unlike the present study, such trials select participants on a very strict criteria. Consequently, he said, 'the benefits and risks of new therapies cannot be extrapolated to patients who were excluded from clinical trials.'

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New calculator should help clinicians diagnose diabetes more accurately

A new calculator should help clinicians classify whether a patient has type 1 or type 2 diabetes, ensuring the patient gets the best treatment and reducing complications (Lynam et al, 2019).

The calculator takes into account available data about the patient, as well as blood test results. It can be used to identify if a person is likely to have type 1 diabetes, to reduce misdiagnosis.

While blood tests or a person's genetic risk of type 1 diabetes may help diagnosis, these tests do not give a diagnosis on their own, and may be interpreted very differently depending on whether or

not a person has other features of type 1 diabetes. The new calculator, currently available in beta format, combines available information from blood tests with a person's age of diagnosis and body mass index for a personalised medicine approach. The calculator was developed by analysing data on 1352 participants with diabetes and tested in a further 582 participants.

Dr Angus Jones, of the University of Exeter Medical School, who led the research, said: 'The right diagnosis in diabetes is absolutely crucial to getting the best outcomes for patients, as treatment is

very different in different types of diabetes. However in some people it can be very difficult to know what type of diabetes they have.

He added: 'Our new calculator can help clinicians by combining different features to give them the probability a person will have type 1 diabetes, and assess whether additional tests are likely to be helpful.'

Lynam A, McDonald T, Hill A et al. Development and validation of multivariable clinical diagnostic models to identify type 1 diabetes requiring rapid insulin therapy in adults aged 18–50 years. *BMJ Open*. 2019 Sep 26;9(9):e031586. <https://doi.org/10.1136/bmjopen-2019-031586>

Exercise capacity may affect cognitive health of survivors of childhood leukaemia

A new study has found a link between reduced exercise capacity and neurocognitive problems in survivors of acute lymphoblastic leukaemia (Phillips et al, 2019).

Survivors of childhood acute lymphoblastic leukaemia are at increased risk of experiencing neurocognitive deficits and reduced exercise capacity as a result of their disease and its treatment. Researchers looked for an association between these outcomes by examining exercise and neuropsychological test results, as well as questionnaire answers, from 341 adult

survivors of childhood acute lymphoblastic leukaemia and 288 healthy controls. The researchers measured how much physical activity survivors could tolerate and how that related to their ability to think, learn, memorize, read and do maths.

Compared with controls, survivors had worse cardiovascular fitness and poorer performance on neuropsychological tests,



Dr Nicholas Phillips, Postdoctoral Research Associate, Epidemiology & Cancer Control, St. Jude Children's Research Hospital, Memphis, Tennessee

including those related to attention, memory and academic skills. After adjusting for age, sex, radiation and chemotherapy treatments, smoking status and physical activity, these increases in exercise capacity were associated with better performance on various neuropsychological tests among survivors.

'Our research suggests that a minor improvement in exercise tolerance, such as going from sitting on the couch and watching TV to walking around the block for 30 minutes a day, can have a significant impact on

survivors' intellectual health,' said Dr Nicholas Phillips, Postdoctoral Research Associate, St. Jude Children's Research Hospital in Memphis, Tennessee.

Phillips NS, Howell CR, Lancot JQ et al. Physical fitness and neurocognitive outcomes in adult survivors of childhood acute lymphoblastic leukemia: A report from the St. Jude Lifetime cohort. *Cancer*. 2019 Oct 21. <https://doi.org/10.1002/cncl.32510>

Effect of fenofibrate on cardiovascular outcomes in people with metabolic syndrome who take statins

A propensity matched cohort study was performed in Korea to investigate whether fenofibrate as an add-on to statin treatment would reduce persistent cardiovascular risk in adults with metabolic syndrome in a real-world setting (Kim et al, 2019).

The study included 29 771 adults (≥ 40 years of age) with metabolic syndrome receiving statin treatment; 2156 participants receiving combined treatment (statin plus fenofibrate) were weighted based on propensity score in a 1:5 ratio with 8549 participants using statin-only treatment. The primary outcome measure was composite cardiovascular events including incident coronary heart disease, ischaemic stroke and death from cardiovascular causes.

The incidence rate of composite cardiovascular events per 1000 person years was 17.7 in the combined treatment group and 22.0 in the statin group. The risk of composite

cardiovascular events was significantly reduced in the combined treatment *vs* the statin group. Significance was maintained in the on-treatment analysis. The risk of incident coronary heart disease, ischaemic stroke and cardiovascular death was lower (but not significantly) in the combined treatment group than the statin group. Participant characteristics did not appear to be associated with the low risk of composite cardiovascular events with combined treatment.

The researchers concluded that the risk of major cardiovascular events was significantly lower in patients taking fenofibrate as an add-on to statin treatment than in those taking statin treatment alone.

Kim NH, Han KH, Choi J, Lee J, Kim SG. Use of fenofibrate on cardiovascular outcomes in statin users with metabolic syndrome: propensity matched cohort study. *BMJ*. 2019 Sep 27;366:l5125. <https://doi.org/10.1136/bmj.l5125>

Effect of infectious disease consultation on outcomes of patients with candida bloodstream infections

Candida bloodstream infection is associated with high mortality. Infectious disease consultation improves outcomes in several infections, as well as those involving multidrug-resistant organisms. A retrospective, single-centre cohort study examined the association between infectious disease consultation and differences in management with mortality in patients with candida bloodstream infections ([https://doi.org/10.1016/S1473-3099\(19\)30405-0](https://doi.org/10.1016/S1473-3099(19)30405-0)).

Data were collected for demographics, comorbidities, predisposing factors, all-cause mortality, antifungal use, central line removal, and ophthalmological and echocardiographic evaluation to assess 90-day all-cause mortality between individuals with and without an infectious disease consultation.

Of 1794 patients assessed for eligibility, 1691 patients with candida bloodstream infection were analysed and included in the study; 776 (45.9%) who had an infectious disease consultation and 915 (54.1%) who did not. 90-day mortality was lower in the infectious disease consultation group than in patients who did not receive an infectious disease consultation. Infectious disease consultation was associated with a hazard ratio of 0.81 (95% confidence interval 0.73–0.91; $P < 0.0001$) for mortality.

The authors concluded that patients with candida bloodstream infection receiving an infectious disease consultation have lower mortality. This might be attributable to these individuals receiving a higher number of non-pharmacological, evidence-based interventions and lower amounts of non-treatment. This suggests that an infectious disease consultation should be an integral part of clinical care of patients with candida bloodstream infection.