following radiation underestimates the incidence in locally advanced cancer. In one series routine bronchoscopy was performed during follow-up, and local control was less than 20% at 1 year [10]. There is clearly a need to improve the locoregional disease eradication rates to impact on survival. This could be achieved by better patient selection and improved radiation technology.

Patient selection: Reports of PET scanning have demonstrated accuracy rates of 80–100% in the detection of nodal metastases compared to approximately 65% for CT and MRI [15]. PET also has the advantage of providing accurate whole body staging. PET can also be used in the process of radiation target volume delineation. The advent of accurate non-invasive staging with PET could have as substantial impact on the use of radiation for this category of patients by removing advanced stage patients from the series of the future. Radiation pulmonary toxicity could contribute to increased morbidity and even mortality. It would be useful to exclude patients in whom the treatment would be more likely to cause damage than improve survival. There are no strict guidelines for such selection, however it may be possible to identify patients likely to have very poor pulmonary function post–radiation in a manner analogous to the preoperative selection of patients. Investigators at the NKI calculate the FEV1 post-RT to be:
FEV1 post-RT = FEV1 pre-RT $\times$ [1-(0.01 $\times$ MLD)] (MLD = Mean lung dose) [11,12].

The influence of new radiation technology: 3-dimensional conformal radiation therapy (3-DCRT) has improved the therapeutic ratio of radiation for lung cancer and has facilitated trials of dose escalation [13]. Early studies identified lung dose safety limits and suggested that elective irradiation of uninvolved nodal areas was unnecessary and potentially toxic. Initially these trials increased dose by prolonging overall treatment time. Accelerated repopulation occurring during this extra time could detract form the benefit of the technology and increased dose. Consequently later studies have increased dose without prolonging time. It is hoped that future trials of escalated dose may demonstrate improved local control and survival.

Radiobiological assessment of a hypofractionated scheme:

	Experimental regimen	Standard regimen
Total Dose/Number of fr	72 Gy/24 fr	60 Gy/30 fr
BED (acute effect/anti-tumour effect)*	102	77
BED (long-term effect)**	137	78
Overall treatment Time (weeks)	5	6

NB: BED denotes Biological Effective Dose, Gy, Gray, fr, fraction.
*Used α/β ratio = 7, **used α/β ratio = 3.3.

At St Luke's Hospital we treated 30 pts with NSCLC with 70Gy in 24 fractions. The KPS was >70% and weight loss <10% in 3 months, with inoperable stage I/II (11 pts) or non-resectable stage IIIa/b, no effusion (19 pts). Initial chemotherapy was used in 13 pts. No more than 30% of the combined lung could receive $\geqslant$25 Gy and the max dose to the spinal cord was <61%. No oesophageal dose limits were used. We noted 8 CR and 11 PR in 27 evaluable pts. Median time to local progression, progression and survival: 18.6, 17.3 and 12.6 months. No grade-4 acute toxicity occurred. 2 pts had grade-3 acute oesophageal toxicity and 1 pt a grade-3 acute lung toxicity. 26 pts were evaluable for long-term toxicity (median follow-up: 9.5 months). Late grade-1 lung toxicity occurred in 5 pts. Late oesophageal toxicity was clinically dominant: Grade 1 in 2 pts, grade 2 in 1 pt and grade 3 in 1 pt. There was a significant association between late oesophageal toxicity and length of circumferential oesophagus receiving 97% of the prescribed dose. If the length was <1 cm late oesophageal toxicity occurred in 0/16 pts vs. 4/10 if it exceeded 1 cm ($p < 0.05$). We redesigned the treatment of patients with oesophageal toxicity and length of circumferential oesophagus receiving 97% of the prescribed dose >1 cm with IMRT to see if this length could be reduced. For 3 of 4 pts IMRT reduced the length without exceeding lung constraints. More data are needed to confirm the feasibility of this strategy, but early toxicity data and tumour response rates are encouraging. This radiobiologically intense high-dose accelerated strategy also has practical and economical advantages.

Control of respiration tumour motion and stereotactic radiosurgery (SRT): Peripheral lung tumours, particularly in the lower lobes move significantly with respiration. They may therefore be undersosed. Various strategies have been adopted to account for and reduce this effect with standard 3-DCRT. Accounting for tumour motion is a prerequisite for SRT. Uematsu from Saitama in Japan treated 50 patients with T1–2N0 NSCLC treated by CT-guided frameless SRT [15]. Of these, 21 patients were medically inoperable and the remainder refused surgery. SRT was 50–60 Gy in 5–10 fractions for 1–2 weeks. Eighteen patients also received conventional radiotherapy. With a median follow-up period of 36 months local progression free survival was 94%. Additional studies which demonstrate great potential for this technology will be presented.

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150 INVITED

Pre and postoperative chemotherapy

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Surgery remains the most important treatment modality for early-stage NSCLC. Yet, even with surgical resection, only 50% of stage I patients achieve long-term survival.

Postoperative adjuvant therapy may be defined as treatment administered to patients who have undergone surgical removal of all known disease, but who are considered at risk for recurrence.

A meta-analysis conducted in the early 1990s demonstrated a 5% improvement in overall survival at 5 years with adjuvant cisplatin-based chemotherapy but the difference did not reach statistical significance.

After 1995, 7 trials were completed in adjuvant setting. Recently, in 2003, Dr Thierry Le Chevalier presented the results of the largest adjuvant trial ever conducted in NSCLC.

Overall survival was statistically significant between the 2 groups with an absolute survival benefit of 4.1% in the chemotherapy group from isolated iv HR = 0.86 [0.76–0.98], $p < 0.03$. This survival benefit would translate into the prevention of approximately 7000 deaths per year if all eligible patients were treated with adjuvant chemotherapy and this is of similar magnitude to that seen in large adjuvant breast cancer studies.

The use of cisplatin-based chemotherapy is considered now as valid option in patients with a good performance status who have undergone complete resection.

Three trials, ECOG 3590, Adjuvant Lung Project Italy (ALPI) and the Big Lung Trial (BLT) failed to demonstrate an improvement in survival. In the Italian study there was a trend towards both improved progression-free and overall survival in resected stage II patients.

The Japan Lung Cancer Research Group (JLCRG) conducted a randomized phase III trial of complete surgical resection followed by 2 years of UFT compared to no treatment in 979 patients with stage I adenocarcinoma.

Overall survival was significantly better in the treatment arm (5-year survival was 87.3% versus 85.4%, $P = 0.035$). Patients with T_2 disease showed even better results.

Recently two very important studies were completed. In Canada, the NCIC JBR10 trial in co-operation with SWOG conducted an adjuvant trial using in the treatment arm the combination Cisplatin–Vinorelbine. The trial randomized 482 patients and the results were in favor of the treatment arm. Five-year survival was 69% versus 54% with an absolute benefit 15% at 5 years, $p = 0.0022$. There was a 30% reduction risk of death, $p = 0.012$.

The CALGB-9633 adjuvant trial used the combination Paclitaxel/Carboplatin in the treatment arm. Adjuvant Pac/Cb is safe (85% completed the 4 cycles treatment). Overall survival for 4 years was 71% and 59% in the chemotherapy and observation groups respectively. The absolute benefit was 12% at 4 years with a 38% reduction risk of death and a p value of 0.028.

Finally, in the Adjuvant Navelbine International Trialist Association (ANITA), 840 patients were randomized to vinorelbine/cisplatin adjuvant therapy or observation following completely resection of stage I (except T1NO), II, or IIIA NSCLC. The median survival was 65.8 months vs 36.5 months in stage 2 patients, and 38.6 months vs 24.1 months in stage IIIA patients. We are talking about an overall survival advantage of 5.1% at 2 years, and 8.6% at 5 years. The ANITA trial confirms the use of adjuvant therapy in patients with respectable NSCLC.

In conclusion, it seems that a significant number of patients with early stage NSCLC have benefit receiving chemotherapy, particularly with new drugs following surgery.

The administration of neoadjuvant chemotherapy for patients with respectable NSCLC has some potential advantages over postoperative chemotherapy.

These advantages must be weighed against concerns regarding increased morbidity and mortality of a combined modality approach and, in case of an ineffective induction regimen, progression of local disease in patients whose tumor could have been resected initially.
An important randomized trial of preoperative chemotherapy to include significant numbers of stage II patients was reported by Depierre et al. While no significant survival benefit was found for the induction treatment, a detailed analysis revealed an increased death rate within the treatment period for the chemotherapy arm. When correcting for this excess of death during treatment, the effect of preoperative chemotherapy turned out to be significant on survival.
Very recently, the randomized phase 3 SWOG S9900 trial, compared preoperative carboplatin and paclitaxel with surgery alone in 335 patients with stage Ib, II, and selected IIIa (non-pN2) NSCLC (abstract LBA7012). Preoperative chemotherapy was tolerated relatively well, with few toxic deaths. About 84% of patients in both the carboplatin/paclitaxel group and the surgery alone group could undergo complete resection. Preoperative chemotherapy improved median progression-free survival (PFS) compared with surgery alone (31 months vs 21 months), though this improvement did not reach statistical significance (HR = 0.80; P = 0.14). There was also a trend toward improved OS in the preoperative chemotherapy group (median OS, 47 months) compared with the surgery alone group (median OS, 40 months) (HR = 0.84; P = 0.32).
Conclusively, the use of preoperative chemotherapy followed by surgery, in patients with stage IB–IIB should be limited to patients enrolled to clinical trials.

Scientific Symposium
Advances in bladder cancer

151 INVITED

Strategies for bladder preservation

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The goal of any organ preservation strategy should be to achieve equivalent cancer survival to extirpative surgery, while maintaining quality of life in the individual patient. Improvement in surgical techniques and the development of continent urinary diversions has resulted in decreased morbidity and better postoperative quality of life for patients undergoing radical cystectomy for muscle-invasive bladder cancer, leading some to suggest that bladder preservation is not necessary.
Although mortality rates with radical cystectomy have decreased by half since the 1990s, survival rates with surgery alone have remained steady, with five-year survival rates of 66% for pathologic stage T2, 35% for T3, and 27% for T4 disease. In addition, up to 15% of patients with muscle-invasive disease will have no pathologic residual disease at the time of cystectomy, indicating the potential curability of select patients with transurethral resection alone. These findings suggest that while bladder preservation can be a viable option to radical cystectomy in selected patients, surgery alone will be successful in only a small percentage of patients. The risk of clinical under staging in around 30% of patients, the limited effectiveness of surgery alone, and the advent of more effective combination chemotherapy has led to a multidisciplinary approach to treatment of bladder cancer with the possibility, in select patients, of bladder preservation.
Surgery, radiotherapy, and chemotherapy should be seen as complementary rather than competing treatment modalities. It appears that the results are not different from those obtained with radical cystectomy.
The goal of a bladder preservation strategy should be to achieve equivalent cancer survival to cystectomy, while maintaining good quality of life.
Randomized studies are needed to evaluate the feasibility of this approach.

152 INVITED

Innovations in radical cystectomy

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Although bladder-sparing treatment protocols have a growing impact radical cystectomy remains the mainstay and therapy of choice for most patients with muscle-invasive bladder cancer. The mortality of the procedure has been reduced dramatically in the last 2 decades, so that even octogenarians can be treated in this manner with similar results. Nevertheless, the morbidity of cystectomy both from postoperative complications and a reduction of quality of life as a result of loss of the bladder remains daunting, and the main impetus of innovations is directed at lowering this.
Immediate postoperative morbidity has been shown to correlate to the volume of cases, and it is lower at high experience centers. It is further reduced by generous correction of blood loss (+10%), routinely using epidural catheters for prolonged pain control, avoiding mechanical bowel preps, and commencing early with enteral nutrition. Laparoscopic cystectomy is a most promising approach to a further reduction in morbidity, but at present the need for urinary diversion still presents as a major obstacle to procedures performed completely intracorporeally. Some laparoscopic techniques are already simplifying standard incisional surgery, such as GIA-stapling of the vesico-prostatic pedicles.
The main rehabilitation problems after cystectomy result from urinary diversion and impaired sexuality. Orthotopic continent urinary diversion has become standard in healthy, well informed patients. Adherence to surgical details such as atraumatic dissection of the urethral stump, avoiding all tubularization of the new-bladder at the anastomosis and fixation of the neobladder to the anterior abdominal wall reduce diurnal and nocturial incontinence to ~15% and ~30% respectively. Nevertheless, a growing body of evidence shows that in elderly, higher risk patients with less pronounced body-image problems simple conduit diversion provides a better quality of life. Nerve-sparing cystectomy continues to provide mixed results only in the effort to retain erectile function but in selected younger patients unilateral nerve preservation in conjunction with supportive measures permits acceptable sexual function. Ongoing attempts of nerve preservation by sparing the prostatic apex, the seminal vesicles and prostatic capsule, and even the entire prostate give better functional results, but are marred by higher rates of local tumor recurrence.
Stage and nodal involvement remain the only independent prognosticators of survival after cystectomy. Negative frozen sections of the distal margin of resection at the prostatic apex or the bladder neck in women are reliable indicators of a low risk of urethral recurrence and hence adequate parameters for urethra-preserving orthotopic bladder substitution. Magnetic resonance lymphangiography using femomagnetic nanoparticles dramatically improves the reliability of preoperative lymph node staging, but extensive pelvic node dissection has been shown to significantly impact survival rates after cystectomy. Although in patients with histologically negative nodes this appears to mainly be a function of stage migration, some patients with positive nodes may actually be cured. The optimal template for pelvic node dissection is still at debate, but prospective studies clearly show that all patients need at least a bilateral, complete endopelvic node dissection; dissection limited to the obturator and hypogastric nodes frequently misses isolated positive nodes.

153 INVITED

Neo-adjuvant or adjuvant chemotherapy

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Objective: Examine the role of systemic chemotherapy before or after cystectomy for muscle-invasive cancer of the urinary bladder.
Material and Methods: Reported individual patient data meta-analyses of neoadjuvant and adjuvant randomized trials are reviewed with focus on effects on survival.
Results: The neoadjuvant analysis was based on 11 trials, 3005 patients; comprising 98% of all patients from known eligible randomised controlled trials. The platinum-based combination chemotherapy had a significant survival benefit with a overall hazard ratio for survival of 0.86 (95%CI: 0.77–0.95, p = 0.003) and a 5% absolute improvement in survival at 5 years. No differences in effect by subgroup could be found.
A corresponding analysis of adjuvant chemotherapy was performed on 491 patients from six trials, representing 66% of patients from all eligible trials. The overall hazard ratio for survival was 0.75 (95%CI: 0.60–0.96, p = 0.019) suggesting a 25% relative reduction in the risk of death for combination chemotherapy compared to that on control. The power of this meta-analysis was limited because of small sample size and questionable trial methodology.
Conclusions: A significant but modest survival benefit is achieved with neoadjuvant chemotherapy. Patients should be informed about this option prior to treatment decisions. Efforts to identify the patients most likely to benefit from this kind of therapy are necessary to optimize its use. The trials of adjuvant chemotherapy indicate a survival benefit but are hampered by questionable methodology.

154 INVITED

Recent advances in metastatic bladder cancer

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M-VAC (cisplatin, methotrexate, adriamycin, vinblastine) combination chemotherapy has been for long time the standard of care in fit patient with advanced urothelial tumors. Throughout the years, many phase III trials