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Abstracts' Service

Certification and Validation of Biosafety Level-2 and Biosafety Level-3 Laboratories in Indian Settings and Common Issues

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With increasing awareness regarding biorisk management worldwide, many biosafety laboratories are being setup in India. It is important for the facility users, project managers and the executing agencies to understand the process of validation and certification of such biosafety laboratories. There are some international guidelines available, but there are no national guidelines or reference standards available in India on certification and validation of biosafety laboratories. There is no accredited government/private agency available in India to undertake validation and certification of biosafety laboratories. Therefore, the reliance is mostly on indigenous experience, talent and expertise available, which is in short supply. This article elucidates the process of certification and validation of biosafety laboratories in a concise manner for the understanding of the concerned users and suggests the important parameters and criteria that should be considered and addressed during the laboratory certification and validation process.

Respiratory Therapy Faculty Knowledge of and Attitudes Toward Interprofessional Education

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Background. Interprofessional education (IPE) improves collaboration and patient care through joint education between health professions. Respiratory therapy (RT) faculty were surveyed to evaluate their knowledge and attitudes toward IPE. We report current opportunities for IPE from faculty and compare responses from associate's, bachelor's, and master's degree programs and profit versus nonprofit institutions.

Methods. We developed an online survey based on IPE literature and questions modified for the RT discipline. The survey was distributed by email to 874 faculty from the Commission on Accreditation for Respiratory Care accredited programs.

Results. The response rate was 33%. Faculty identified IPE as an important component of RT education (n = 207, 80%) but reported challenges in integrating IPE into current curriculum. Overall, communication was ranked as the most important IPE competency (n = 104, 39%) and ethics least important (n = 131, 49%). When asked how many credit hours are required to teach IPE, 48% of respondents reported that they were unsure of an appropriate time requirement. Significant differences between associate's and bachelor's/master's degree program faculty were found on the following topics: institutional resources needed for IPE ($P < .001$), faculty availability ($P < .001$), curriculum availability for IPE ($P = .02$), and importance of including IPE at academic health center campuses ($P < .001$).

Conclusions. IPE is recognized as an important component of RT education by all faculty respondents. However, significant differences in knowledge and attitudes toward IPE exist between faculty in associate's versus bachelor's/master's degree programs. Revisiting the current accreditation standards program may allow IPE to take a more prominent role in RT curricula.

Diaphragm Muscle Thinning in Subjects Receiving Mechanical Ventilation and Its Effect on Extubation

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Background. Diaphragm muscle weakness and atrophy are consequences of prolonged mechanical ventilation. Our purpose was to determine whether thickness of the diaphragm (TDI) changes over time after intubation and whether the degree of change affects clinical outcome.

Methods. For this prospective, longitudinal observational study, we identified subjects who required mechanical ventilation and measured their TDI by ultrasonography. TDI was measured at baseline and repeated 72 h later and then weekly until the subject was either liberated from mechanical ventilation, was referred for tracheostomy, or died. The analysis was designed to determine whether baseline TDI and change in TDI affect extubation outcome.

Results. Of the 57 subjects who underwent both diaphragm measurements at 72 h, 16 died, 33 were extubated, and 8 underwent tracheostomy. Only 14 subjects received mechanical ventilation for 1 week, and 2 subjects received mechanical ventilation for 2 and 3 weeks. Females had significantly thinner baseline TDI (P = .008). At 72 h, TDI had decreased in 84% of subjects. We found no significant association between the rate of thinning and sex (P = .68), diagnosis of COPD (P = .36), current smoking (P = .85), or pleural effusion (P = .83). Lower baseline TDI was associated with higher likelihood of extubation: 12.5% higher for every 0.01-cm decrease in TDI (hazard ratio 0.875, 95% CI 0.80–0.96, P = .003). For every 0.01-cm decrease in TDI at 72 h, the likelihood of extubation increased by 17% (hazard ratio 0.83, 95% CI 0.70–0.99, P = .041).

Conclusions. Although most of the subjects showed evidence of diaphragm thinning, we were unable to find a correlation with outcome of extubation failure. In fact, the thinner the diaphragm at baseline and the greater the extent of diaphragm thinning at 72 h, the greater the likelihood of extubation. Thickening ratio or other measurement may be a more reliable indicator of diaphragm dysfunction and should be explored.

Predictors for Hilar/intrapulmonary Lymph Node Metastasis in Discrete Type of Clinical N1 Non-small Cell Lung Cancer

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Objective. Accurate preoperative evaluation of lymph nodes can provide optimal treatment for patients. However, in patients with clinical N1 disease (cN1) non-small cell lung cancer (NSCLC), no suitable predictor has been identified for hilar/intrapulmonary lymph node metastasis (pathological N1 disease; pN1). The purpose of this study was to identify pN1 in cN1 NSCLC patients.

Methods. We retrospectively reviewed the clinicoradiological features of 109 patients with a discrete type of cN1 NSCLC who had undergone complete resection at our institution from 2004 to 2015. The association between clinicoradiological variables and nodal status was analyzed to identify predictors for pN1.

Results. The cohort consisted of 77 males and 32 females, ranging in age from 39 to 84 years. The breakdown by pathological N category was 40 (37%) pN0, 41 (38%) pN1, and 28 (25%) pN2 patients. Maximum lymph node diameter was identified as a significant predictor for pN1, with an odds ratio of 1.25 (P = 0.010). When limited to 63 patients who underwent positron emission tomography (FDG-PET) at our institution, the maximum standardized uptake value (SUV_{max}) of the lymph node was an independent predictor, with an odds ratio of 1.91 with logistic regression analysis (P = 0.004). The size of lymph node and the SUV_{max} were significant factors for pN1, with optimal cut-off values of 13 mm and 4.28, respectively.

Conclusions. Among the patients with cN1, maximum lymph node size and SUV_{max} of the FDG-PET were significant predictors for pN1.

Prognostic Significance of Neutrophil–lymphocyte Ratios in Large Cell Neuroendocrine Carcinoma

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Objectives. Large cell neuroendocrine carcinomas (LCNECs) are rare neuroendocrine pulmonary malignancies with poor survival. Towards the goal of identifying a useful prognostic marker for LCNEC, we examined the prognostic significance of the neutrophil–lymphocyte ratio (NLR) in LCNEC patients after complete resection. The NLR is a potential predictive indicator in other cancers and can be easily determined at low cost.

Methods. We retrospectively reviewed the perioperative clinical and laboratory data of patients who underwent complete resection for LCNEC between 1995 and 2014. Correlations between the preoperative NLR and clinicopathological parameters were determined to assess its prognostic significance.

Results. Our study consisted of 26 patients, most of whom were men (88.5%) with a median age of 68.8 years. The median follow-up time was 54.4 months. Univariate analysis identified 3 clinically significant overall survival predictors: serum albumin level [≥ 4.0 g/dL (5-year overall survival rate; 80.0%) vs. <4.0 g/dL (30.0%), $p = 0.048$], pathological T stage [T1 and T2 (79.6%) vs. T3 and T4 (0%), p = 0.001], and preoperative NLR [<1.7 (90.9%) vs. ≥ 1.7 (51.7%), $p = 0.012$]. In a multivariate analysis, the NLR was an independent prognostic factor for overall survival (hazard ratio 8.559, 95% confidence interval 1.783–80.230, $p = 0.011$).

Conclusions. The preoperative NLR inversely correlates with post-resection survival rates in patients with LCNEC and thus is a viable prognostic marker in LCNEC.

PET-guided Treatment in Patients with Advanced-stage Hodgkin's Lymphoma (HD18): Final Results of An Open-label, International, Randomised Phase 3 Trial by the German Hodgkin Study Group

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Background. The intensive polychemotherapy regimen eBEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone in escalated doses) is very active in patients with advanced-stage Hodgkin's lymphoma, albeit at the expense of severe toxicities. Individual patients might be cured with less burdensome therapy. We investigated whether metabolic response determined by PET after two cycles of standard regimen eBEACOPP (PET-2) would allow adaption of treatment intensity, increasing it for PET-2-positive patients and reducing it for PET-2-negative patients.

Methods. In this open-label, randomised, parallel-group phase 3 trial, we recruited patients aged 18–60 years with newly diagnosed, advanced-stage Hodgkin's lymphoma in 301 hospitals and private practices in Germany, Switzerland, Austria, the Netherlands, and the Czech Republic. After central review of PET-2, patients were assigned (1:1) to one of two parallel treatment groups on the basis of their PET-2 result. Patients with positive PET-2 were randomised to receive six additional cycles of either standard eBEACOPP (8 × eBEACOPP in total) or eBEACOPP with rituximab (8 × R-eBEACOPP). Those with negative PET-2 were

randomised between standard treatment with six additional cycles of eBEACOPP (8 × eBEACOPP) or experimental treatment with two additional cycles (4 × eBEACOPP). A protocol amendment in June, 2011, introduced a reduction of standard therapy to 6 × eBEACOPP; after this point, patients with positive PET-2 were no longer randomised and were all assigned to receive 6 × eBEACOPP and patients with negative PET-2 were randomly assigned to 6 × eBEACOPP (standard) or 4 × eBEACOPP (experimental). Randomisation was done centrally using the minimisation method including a random component, stratified according to centre, age (<45 *vs* ≥ 45 years), stage (IIB, IIIA *vs* IIIB, IV), international prognostic score (0–2 *vs* 3–7), and sex. eBEACOPP was given as previously described; rituximab was given intravenously at a dose of 375 mg/m^2 (maximum total dose 700 mg). The primary objectives were to show superiority of the experimental treatment in the PET-2-positive cohort, and to show non-inferiority of the experimental treatment in the PET-2-negative cohort in terms of the primary endpoint, progression-free survival. We defined non-inferiority as an absolute difference of 6% in the 5-year progression-free survival estimates. Primary analyses in the PET-2-negative cohort were per protocol; all other analyses were by intention to treat. This trial was registered with ClinicalTrials.gov, number NCT00515554.

Findings. Between May 14, 2008, and July 18, 2014, we recruited 2101 patients, of whom 137 were found ineligible before randomisation and a further 19 were found ineligible after randomisation. Among 434 randomised patients (217 per arm) with positive PET-2, 5-year progression-free survival was 89·7% (95% CI 85·4–94·0) with eBEACOPP and 88·1% (83·5–92·7) with R-eBEACOPP (log-rank p=0·46). Patients with negative PET-2 randomly assigned to either 8 × eBEACOPP or 6 × eBEACOPP (n=504) or 4 × eBEACOPP (n=501) had 5-year progression-free survival of 90·8% (95% CI 87·9–93·7) and 92·2% (89·4–95·0), respectively (difference 1·4%, 95% CI–2·7 to 5·4). 4 × eBEACOPP was associated with fewer severe infections (40 [8%] of 498 *vs* 75 [15%] of 502) and organ toxicities (38 [8%] of 498 *vs* 91 [18%] of 502) than were 8 × eBEACOPP or 6 × eBEACOPP in PET-2-negative patients. Ten treatment-related deaths occurred: four in the PET-2-positive cohort (one [<1%] in the 8 × eBEACOPP group, three [1%] in the 8 × R-eBEACOPP group) and six in the PET-2-negative group (six [1%] in the 8 × eBEACOPP or 6 × eBEACOPP group).

Interpretation. The favourable outcome of patients treated with eBEACOPP could not be improved by adding rituximab after positive PET-2. PET-2 negativity allows reduction to only four cycles of eBEACOPP without loss of tumour control. PET-2-guided eBEACOPP provides outstanding efficacy for all patients and increases overall survival by reducing treatment-related risks for patients with negative PET-2. We recommend this PET-2-guided treatment strategy for patients with advanced-stage Hodgkin's lymphoma.