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Haemorrhagic Complications and Symptomatic Venous Thromboembolism in Interventional Tumour Ablations: The Impact of Peri-interventional Thrombosis Prophylaxis

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Abstract
Aim The aim of this study was to assess the rates of haemorrhagic and thrombotic complications in patients undergoing interventional tumour ablation with and without peri-interventional low-molecular-weight heparin (LMWH) thrombosis prophylaxis.
Methods Patients presented with primary and secondary neoplastic lesions in the liver, lung, kidney, lymph nodes and other locations. A total of 781 tumour ablations (radiofrequency ablation, $n = 112$; interstitial brachytherapy, $n = 669$) were performed in 446 patients over 22 months; 260 were conducted under peri-interventional thrombosis prophylaxis with LMWH (H-group;) and 521 without this (NH-group, in 143 of these, LMWH was given post-interventionally).
Results Sixty-three bleeding events occurred. There were significantly more bleedings in the H-group than in the NH-group (all interventions, 11.66 and 6.26 %, $p = 0.0127$; liver ablations, 12.73 and 7.1 %, $p = 0.0416$). The rate of bleeding events Grade $\geq$ III in all procedures was greater by a factor of >2.6 in the H-group than in the NH-group (4.64 and 1.73 %, $p = 0.0243$). In liver tumour ablations, the corresponding factor was about 3.3 (5.23 and 1.54 %, $p = 0.028$). In uni- and multivariate analyses including covariates, the only factor constantly and significantly associated with the rate of haemorrhage events was peri-interventional LMWH prophylaxis. Only one symptomatic lung embolism occurred in the entire cohort (NH-group). The 30- and 90-day mortalities were significantly greater in the H-group than in the NH-group.
Conclusions Peri-interventional LMWH thrombosis prophylaxis should be considered with caution. The rate of clinically relevant thrombotic events was extremely low.

Keywords Ablation · Complications · Bleeding events · Heparin · LMWH · RFA · Brachytherapy

Introduction

In hospital patients, venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE), is an important preventable cause of morbidity and mortality. Over the past decades this has led to the adoption of recommendations for VTE prophylaxis in current guidelines [1, 2, 5]. Cancer patients have twice the incidence of DVT compared with those without cancer [14]. Overall, the incidence of VTE was 2.0 and 0.6 % for PE among over 40 million cancer patients hospitalized in the United States from 1979 to 1999 [14]. There are large differences between the various types of cancer. One study [14] showed that patients with pancreatic cancer had the highest relative risk of 4.65 compared with non-cancer hospitalized controls, whereas patients with bladder cancer had a relative risk of 1.07, scarcely higher than that of the non-cancer control group. However, this study did not discriminate between invasive and non-invasive treatments

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or procedures. Interestingly, and in contrast to current guidelines, a recent meta-analysis reached the conclusion that in over 16,000 patients the use of heparin-based VTE prevention did not lead to a significant reduction in symptomatic DVT, PE, fatal PE or total mortality, although the cohort included patients with and without cancer [13].

Over and above heparin-induced thrombocytopenia [4], peri-operative administration of low-molecular-weight heparin (LMWH) leads to an increased risk of haemorrhagic complications. In patients undergoing hepatopancreatobiliary surgery, the preoperative administration of LMWH led to a lower incidence of thromboembolic events (1.1 % with LMWH, 6.1 % without) but to a higher rate of bleeding episodes requiring intervention (10.9 % with LMWH, 3.1 % without) [6].

Owing to the inception of an interdisciplinary oncological gastrointestinal ward and the harmonization of the standard operating procedures with the surgical department, most of the cancer patients treated from March 2013 until November 2013 received peri-interventional thrombosis prophylaxis with LMWH. A higher rate of minor and major bleeding events was noticed, and therefore the relevant standard procedure was changed to a much more restrictive regimen regarding the use of LMWH. After this, all patients treated with or without peri-interventional LMWH from January 2013 to October 2014 were analysed for bleeding events and symptomatic VTE.

Patients and Methods

Patient Population and Eligibility Criteria

Data from 781 extracranial interstitial interventions in 446 patients treated either by high-dose-rate interstitial brachytherapy (iBT, $N = 669$) or by radiofrequency ablation (RFA, $N = 112$) from January 2013 to October 2014 were analysed for haemorrhagic complications and symptomatic venous thromboembolism events.

Patients presented with primary and secondary neoplastic lesions in the liver, lung, kidney, lymph nodes and other locations (for patients and treatment characteristics, see Table 1).

Two hundred and sixty interventions were conducted that included peri-interventional thrombosis prophylaxis with low-molecular-weight heparin (H-group), whereas 521 interventions were performed without this (NH-group). In 143 of these 521 interventions, LMWH was given post-interventionally. All patients were mobilized early (4 h after the intervention). Peri-interventional LMWH dosing was defined as any administration at least 24 h before intervention. For thrombosis prophylaxis, we usually prescribed Dalteparin (Fragmin P forte®) once a day for the entire hospital stay, starting from the preinterventional evening.

The study was approved by the local ethics committee (Ethics Committee of the Medical Faculty, University of Magdeburg, 185/14).

Ablation Methods

Patients were treated by either radiofrequency ablation (RFA) or interstitial brachytherapy (iBT) under guidance with magnetic resonance imaging (MRI) or computed tomography (CT). In RFA, thermoablation was performed with an AngioDynamics generator (Latham, NY) and correspondent RF-applicators (RITA Starburst). For iBT, between one and eight 6F-angiography sheaths were placed in the liver, the lung or other extracranial body regions harbouring 6F-brachytherapy catheters guiding the iridium-192 point source during the treatment session. This ablation method has been described in detail elsewhere [8–12].

The tracks of the radiofrequency applicators were coagulated during retreatment following the manufacturer's instructions. The tracks of the brachytherapy catheters were closed with Gelaspone plugs introduced over the sheaths during the retraction.

Interventions were performed under mild analgosedation and local anaesthesia.

Assessments and Statistical Methods

Events were recorded according to the Common Terminology Criteria for Adverse Events (version 4.0) with minor adaptations regarding Grade I and II bleeding events (Grade I, asymptomatic haematoma <1 cm; Grade II, symptomatic haematoma or haematoma ≥ 1 cm). The complete patient documentation, including admission and discharge diagnoses, discharge summary, the health and medical records of each patient and the peri- and post-interventional imaging (CT, MRI, sonography) were included in the evaluation. Therefore, haematoma or active bleeding was diagnosed with ultrasound and/or computed tomography and/or magnetic resonance imaging.

Peri- and post-interventional LMWH dosing was documented and correlated with bleeding events. Clinical and paraclinical parameters and cofactors such as bleeding or clotting disorders, coagulation status, the Padua Prediction Score for the risk of VTE were recorded [3].

The primary variables in this analysis were as follows: (i) the rate of bleeding events (any grade), (ii) the rate of bleeding events requiring intervention (Grade III and above) and (iii) the frequency of VTE. These were compared for the patients either with (H-group) or without (NH-group) peri-interventional LMWH administration. Secondary endpoints were the rate of bleeding events in

Table 1 Patients and treatment characteristics

Patients	$N = 446$
Interventions	$N = 781$ (100.0 %)
Primary cancer	$n = 308$ (39.4 %)
Colorectal cancer	$n = 104$ (13.3 %)
Hepatocellular carcinoma	$n = 96$ (12.3 %)
Cholangiocellular cancer	$n = 50$ (6.4 %)
Breast cancer	$n = 50$ (6.4 %)
Renal cell cancer	$n = 30$ (3.8 %)
Liver cancer	$n = 24$ (3.1 %)
Gastroenteropancreatic neuroendocrinal tumour	$n = 119$ (15.2 %)
Other	
Clotting disorders	$n = 22$ (2.9 %)
Thrombopenic	$n = 14$ (1.8 %)
Thrombophilic	$n = 8$ (1.0 %)
Cirrhosis	$n = 98$ (12.5 %)
Child–Pugh stage B	$n = 21$ (2.7 %)
Padua score <4	$n = 229$ (29.3 %)
Padua score ≥4	$n = 552$ (70.7 %)
RFA	$n = 112$ (14.3 %)
iBT	$n = 669$ (85.8 %)
Peri-interventional LMWH dosing	$n = 260$ (33.3 %)
Hospital stay	4.8 days (95 % CI 4.6–5.1, range 2–15)

liver interventions and the 30- and 90-day mortality. In order to address the fact that some of the patients had several treatments, generalised mixed linear models (software SAS, Version 9.4, Proc GLIMMIX) were used, with the number of bleeding events or bleeding events requiring intervention as the dependent variable, a random intercept for each patient, and the presence or absence of peri-interventional LMWH as fixed factor. In secondary analyses, additional covariates were considered in the model (only one at a time, because of the limited number of events). Furthermore, the analyses were repeated in the subgroup of liver interventions.

The 30- and 90-day mortality and survival times were analysed at the patient level (considering only the first treatment for each patient) by using the χ^2 test, log-rank tests and Cox regression as appropriate, comparing patients with and without bleeding events. These analyses were performed with the programme suite IBM SPSS Statistics 22.0.

p values below 0.05 were considered significant at an exploratory level of this study.

Results

In all 781 interventions, 63 haemorrhagic events of any severity occurred (8.1 %). In 33 of 521 interventions in patients without peri-interventional LMWH dosing (NH-group), bleeding of any grade occurred corresponding to a bleeding rate of 6.3 %. Compared with 30 interventions with haemorrhagic events of any grade in patients with peri-interventional LMWH dosing (H-group, 11.7 %), this difference was statistically significant ($p = 0.0127$). In liver interventions, there were 23 of 325 interventions in the NH-group (7.1 %) compared with 22 of 173 in the H-group (12.73 %; $p = 0.046$).

Severe bleeding (Grade III and above) occurred in 9 of 521 interventions (all sites) in the NH-group (1.7 %) compared with 12 of 260 interventions in the H-group (4.64 %, $p = 0.024$). In liver interventions, there were 5 of 325 interventions in the NH-group (1.54 %) compared with 9 of 173 in the H-group (5.23 %; $p = 0.028$).

The rate of bleeding events of any grade was higher after RFA (16 of 112 interventions, 14.29 %) than after iBT ablation (47 of 669 interventions, 7.03 %; $p = 0.0149$). In liver interventions, there were 11 such events (19.6 %) in 56 RFA interventions and 34 events (7.7 %) in 441 iBT interventions ($p = 0.0054$). No differences were seen in respect of the proportion of patients receiving peri-interventional LMWH dosing between the treatments RFA and iBT (iBT 33.0 %, RFA 34.8 %, $p = 0.710$). The frequency of severe bleeding events was not significantly different between the RFA and iBT patients ($p = 0.5351$).

Peri-interventional LMWH dosing was the only constantly and significantly contributing factor to increase both

the total and severe bleeding rate in a secondary analysis, including covariates known or suspected to increase, directly or indirectly, the bleeding rate (see Tables 2, 3). The treatment (RFA or iBT) proved to be an independent risk factor for the total bleeding rate. However, this was not the case for severe bleeding events. Thrombopenic disorders were more frequent in patients with haemorrhagic complications (5 % for those with complications, 1 % for those without; $p = 0.03$, Table 4).

No bleeding events occurred in patients with post-interventional LMWH dosing (143 interventions). Symptomatic VTE occurred in only one patient without peri-interventional LMWH dosing, diagnosed 2 months after the intervention.

The all-cause 30-day mortality rate was 1.2 % (5 of 431 patients) and the 90-day rate was 3.5 % (14 of 404 patients). In uni- and multivariate analysis, bleeding events of the Common Terminology Criteria for Adverse Events (CTCAE) Grade $\geq$ III were strongly associated with the 30-day mortality ($p < 0.0001$, odds ratio 53.4), whereas no significant association with age was found ($p = 0.162$ and 0.374 in uni- and multivariate analysis respectively). Therefore, the 30- and 90-day mortality rates among patients without, or with mild, bleeding events were 0.5 and 2.3 % (2 of 418 and 9 of 391 patients), while among patients with bleeding events of CTCAE Grade $\geq$ III it were 23.1 and 38.5 % (3 of 13 and 5 of 13 patients). These differences were significant ($p < 0.0001$). The specific causes of death in the group of patients with severe haemorrhagic complications were subsequent bleeding complications due to the following: (1) uncontrolled oozing in the pelvicocealiceal system after brachytherapy of a renal cell carcinoma, (2) a colon perforation distant from the liver irradiation zone after urgent embolisation of a large intrahepatic haematoma following brachytherapy of liver metastases, (3) an infected intrahepatic haematoma with subsequent sepsis and multiple organ failure after RFA of liver metastases, (4) an uncontrollable bleeding into the biliary tract despite angiography and endoscopy after iBT of the liver, (5) haematothorax after RFA of lung metastases, with pneumonia and sepsis after discharge.

Discussion

To our knowledge, this is the first study specifically addressing the correlation between bleeding events (and symptomatic VTE) and the administration of peri-operative LMWH in cancer patients undergoing interventional, image-guided tumour-directed treatments.

The analysis led to three principal results. First of all, the analysis of this large patient cohort proves the increased risk of bleeding (both 'all events' and 'severe events') associated with the peri-interventional administration of LMWH. The analysis showed a 2.7-fold increase in the frequency of such severe events after peri-interventional LMWH dosing in the entire patient cohort and a 3.4-fold increase in after liver interventions. This is comparable to

Table 2 Haemorrhagic complications of any severity

Covariate	Mean value (95 % CI)	Bleeding rate: Interaction between peri-interventional LMWH dosing and covariate, p value		Influence of peri-interventional LMWH dosing on bleeding rate adjusted for covariate, p value		Influence of covariate on bleeding rate adjusted for peri-interventional LMWH dosing, p value		Influence of covariate only, p value	
Interventions		All	Liver	All	Liver	All	Liver	All	Liver
Modality (RFA/iBT)	n.a.	0.4110	0.8294	**0.0137**	**0.0145**	**0.0172**	**0.0057**	**0.0149**	**0.0054**
Number of Catheters (iBT)	2.71 (1–9)	0.2001	0.1463	**0.0198**	**0.0422**	0.5421	0.5201	0.5075	0.5076
Thrombocytes (Gpt/l, 176–391)	212 (204–220)	0.6166	0.9062	**0.0120**	**0.0426**	0.4926	0.8879	0.5428	0.8025
Haemoglobin (mmol/l, 7.2–9.6)	8.04 (7.95–8.14)	0.8232	0.8904	**0.0138**	**0.0474**	0.4882	0.3768	0.4276	0.3168
Haematocrit (l/l, 0.35–0.45)	0.39 (0.39–0.39)	0.8838	0.7455	**0.0129**	**0.0434**	0.6889	0.5186	0.6607	0.4840
Prothrombin time (>70 %)	108 (106–109)	0.3096	0.8845	**0.0160**	**0.0405**	0.1335	0.3270	*0.0762*	0.2537
Creatinine (μmol/l)	89 (82–95)	0.6525	0.6234	**0.0074**	**0.0235**	0.2435	0.2899	0.3163	0.3779
Cirrhosis	n.a.	0.7009	0.7019	**0.0134**	**0.0388**	0.2696	0.3891	0.2487	0.4311
Cirrhosis CHILD–PUGH B	n.a.	0.6024	0.9234	**0.0135**	**0.0414**	0.3558	0.7461	0.3208	0.7576

Generalised linear mixed model. Interaction between peri-interventional LMWH dosing and different covariates. Influence of LMWH adjusted for covariates and vice versa and of covariates alone. p values <0.05 (bold letters) indicate statistical significance. p value at the border of significance ($p < 0.1$) is in italic

Table 3 Severe haemorrhagic complications

Covariate	Mean value (95 % CI)	Bleeding rate: Interaction between peri-interventional LMWH dosing and covariate, *p* value		Influence of peri-interventional LMWH dosing on bleeding rate adjusted for covariate, *p* value		Influence of covariate on bleeding rate adjusted for peri-interventional LMWH dosing, *p* value		Influence of covariate only, *p* value	
Interventions		All	Liver	All	Liver	All	Liver	All	Liver
Modality (RFA/iBT)	n.a.	0.4563	0.9079	**0.0248**	**0.0281**	0.5669	0.2469	0.5351	0.2357
Number of Catheters (iBT)	2.71 (1–9)	0.4867	0.8657	**0.0241**	**0.0281**	0.8403	0.8923	0.8041	0.8778
Thrombocytes (Gpt/l, 176–391)	212 (204–220)	0.2422	0.5330	**0.0216**	**0.0224**	0.1773	0.1658	0.1987	0.2095
Haemoglobin (mmol/l, 7.2–9.6)	8.04 (7.95–8.14)	0.6401	0.5974	**0.0247**	**0.0284**	0.8841	0.9593	0.8203	0.8552
Haematocrit (l/l, 0.35–0.45)	0.39 (0.39–0.39)	0.7044	0.7844	**0.0243**	**0.0279**	0.9896	0.9443	0.9902	0.9895
Prothrombin time (>70 %)	108 (106–109)	0.1718	0.2555	**0.0202**	**0.0168**	0.4277	0.8612	0.2738	0.9942
Creatinine (µmol/l)	89 (82–95)	0.8958	0.5906	**0.0146**	**0.0144**	0.7404	0.5808	0.8160	0.7184
Cirrhosis	n.a.	0.7635	0.7331	**0.0245**	**0.0287**	0.8350	0.7809	0.8083	0.7212
Cirrhosis CHILD–PUGH B	n.a.	0.7364	0.9234	**0.0262**	**0.0274**	*0.0871*	0.4657	*0.0707*	0.4853

Generalised linear mixed model. Interaction between peri-interventional LMWH dosing and different covariates. Influence of LMWH adjusted for covariates and vice versa and of covariates alone. *p* values <0.05 (bold letters) indicate statistical significance. *p* values at the border of significance ($p < 0.1$) are in italics

Table 4 Covariates across groups

Covariate	Peri-interventional LMWH dosing			Haemorrhagic complication			Severe haemorrhagic complication		
	Yes	No	*p*	Yes	No	*p*	Yes	No	*p*
Haematocrit [l/l, 0.35–0.45]	0.39	0.39	0.64	0.39	0.39	0.67	0.39	0.39	0.69
Haemoglobin [mmol/l, 7.2–9.6]	8.0	8.1	0.14	8.0	8.0	0.77	8.1	8.0	0.92
Thrombocytes (Gpt/l, 176–391)	213	212	0.84	205	213	0.36	204	212	0.56
Prothrombin time (>70 %)	107	108	0.79	106	108	0.17	107	108	0.97
Creatinine (µmol/l)	90	88	*0.07*	88	89	0.96	91	88	0.62
Cirrhosis	11 %	11 %	0.98	14 %	10 %	0.41	13 %	11 %	0.82
Child–Pugh stage B	3 %	2 %	0.77	4 %	2 %	0.39	8 %	2 %	0.16
Padua score ≥4	78 %	72 %	0.17	81 %	73 %	0.29	85 %	74 %	0.33
Thrombopenic disorder	–	–	–	5 %	1 %	**0.03**	7 %	1 %	*0.09*
Thrombophilic disorder	1.8 %	0.2 %	**0.037**	0.9 %	0.7 %	0.82	–	–	–

Estimators of marginal means from mixed linear models or estimates of percentages from generalized linear mixed models. *p* values <0.05 (bold letters) indicate statistical significance. *p* values at the border of significance ($p < 0.1$) are in italics

findings in hepatopancreatobiliary surgery [6]. In an earlier study addressing complications in interstitial brachytherapy of liver neoplasms, severe bleeding was linked to the advanced liver cirrhosis [9]. In that study, peri-interventional LMWH dosing was not a standard procedure and the number of interventions in patients with Child–Pugh B cirrhosis was higher than in our trial (3.5 vs 2.7 %). Nonetheless, we observed a trend towards an effect of Child–Pugh B cirrhosis on the severe bleeding rate in this trial too (see Table 3).

Secondly, only one symptomatic venous thromboembolic event (lung embolism) occurred in all 781 interventions (0.13 %). The low invasiveness of the therapeutic procedures and the early mobilization 3–4 h after the intervention as a standard operating procedure at our department may have been the contributing factors.

Thirdly, patients with severe bleeding rates showed very high 30- and 90-day mortality rates. Therefore, we attribute the peri- and short-term post-interventional mortality mainly to severe bleeding and its complications, leading to

a 46-fold increase in the 30-day mortality and to a 17-fold increase in the 90-day mortality. The mortality rates were higher than reported for upper gastrointestinal bleeding, even though a broad range among centres has been reported [7]. This is most probably due to the impact of cancer on the patient's general condition, and to cancer-related coagulopathies and other comorbidities in this elderly patient cohort, enhancing the negative impact of volume loss, anaemia and inflammation. The causes of death were uncontrollable, ooze bleedings that could not be embolised, infections most probably related to haematoma, and a colon perforation probably driven by ischaemia due to volume loss-related centralization effects. Therefore, and to reduce mortality, aggressive early interventions in these patients are indicated. Such interventions may include early blood transfusion, early angiography or surgery (if surgery appears promising and interventional embolisation fails). Furthermore, close monitoring of haematomas for signs of infections is necessary and urgent antibiotic/anti-inflammatory treatment should be provided.

However, in some patients, peri-interventional anticoagulation (e.g. as a bridging therapy in patients with vitamin K antagonists medication) cannot be evicted. In these patients, the indication to interstitial treatments and the conduction of such demand a comprehensive and prudent proceeding.

Conclusion

Our findings show that a "blanket" peri-interventional LMWH prophylaxis for all patients cannot be recommended in the cancer patients undergoing radiological interventions. On the contrary, it should be prescribed with caution, and those patients receiving it require particularly close monitoring for bleeding events. Patients with severe bleeding events need aggressive treatment to avoid, or to treat, a relevant volume loss or the development of large haematomas.

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Compliance with Ethical Standards

Conflict of interest There are no conflicts of interest to state.

Ethical Standards The study was conducted in accordance with the protocol, with the ethical principles that have their origin in the Declaration of Helsinki and with ICH-GCP. The study protocol and all study-related documentation were approved by the relevant committee (Ethic Committee of the Medical Faculty, University of Magdeburg, 185/14).

References

1. Lowe GDO (Chairman of the THRIFT Consensus group). Risk of and prophylaxis for venous thromboembolism in hospital patients. Thromboembolic Risk Factors (THRIFT) Consensus Group. BMJ. 1992;305(6853):567–74.
2. Anderson FA Jr, Wheeler HB, Goldberg RJ, Hosmer DW, Forcier A, Patwardhan NA. Physician practices in the prevention of venous thromboembolism. Ann Intern Med. 1991;115(8):591–5.
3. Barbar S, Noventa F, Rossetto V, et al. A risk assessment model for the identification of hospitalized medical patients at risk for venous thromboembolism: the Padua Prediction Score. J Thromb Haemost: JTH. 2010;8(11):2450–7.
4. Battistelli S, Genovese A, Gori T. Heparin-induced thrombocytopenia in surgical patients. Am J Surg. 2010;199(1):43–51.
5. Clagett GP, Anderson FA Jr, Heit J, Levine MN, Wheeler HB. Prevention of venous thromboembolism. Chest. 1995;108(4 Suppl):312S–34S.
6. Doughtie CA, Priddy EE, Philips P, Martin RC, McMasters KM, Scoggins CR. Preoperative dosing of low-molecular-weight heparin in hepatopancreatobiliary surgery. Am J Surg. 2014;208(6):1009–15.
7. Jairath V, Martel M, Logan RF, Barkun AN. Why do mortality rates for nonvariceal upper gastrointestinal bleeding differ around the world? A systematic review of cohort studies. Can J Gastroenterol. 2012;26(8):537–43.
8. Mohnike K, Wieners G, Schwartz F, et al. Computed tomography-guided high-dose-rate brachytherapy in hepatocellular carcinoma: safety, efficacy, and effect on survival. Int J Radiat Oncol Biol Phys. 2010;78(1):172–9.
9. Mohnike K, Wolf S, Damm R, et al. Radioablation of liver malignancies with interstitial high-dose-rate brachytherapy: complications and risk factors. Strahlentherapie Onkol. 2016;192(5):288–96.
10. Peters N, Wieners G, Pech M, et al. CT-guided interstitial brachytherapy of primary and secondary lung malignancies: results of a prospective phase II trial. Strahlentherapie Onkol. 2008;184(6):296–301.
11. Ricke J, Mohnike K, Pech M, et al. Local response and impact on survival after local ablation of liver metastases from colorectal carcinoma by computed tomography-guided high-dose-rate brachytherapy. Int J Radiat Oncol Biol Phys. 2010;78(2):479–85.
12. Ricke J, Wust P, Wieners G, et al. Liver malignancies: CT-guided interstitial brachytherapy in patients with unfavorable lesions for thermal ablation. J Vasc Intervent Radiol JVIR. 2004;15(11):1279–86.
13. Spencer A, Cawood T, Frampton C, Jardine D. Heparin-based treatment to prevent symptomatic deep venous thrombosis, pulmonary embolism or death in general medical inpatients is not supported by best evidence. Intern Med J. 2014;44(11):1054–65.
14. Stein PD, Beemath A, Meyers FA, Skaf E, Sanchez J, Olson RE. Incidence of venous thromboembolism in patients hospitalized with cancer. Am J Med. 2006;119(1):60–8.